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(57) Abstract

The present invention relates generally to identification of proteins, designated TIH proteins, that interact with casein kinase I isoforms and to isolation of polynucleotides encoding the same.

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Materials and Methods Relating To Proteins That Interact With Casein Kinase I

This application is a continuation-in-part of U.S. Patent Application Serial No.08/184,605, filed January 21, 1994.

FIELD OF THE INVENTION

The present invention relates generally to identification of proteins, herein designated TIH proteins, that interact with casein kinase I isoforms and to isolation of polynucleotides encoding the same.

BACKGROUND

Protein kinases are post-translational, enzymatic regulators of cellular metabolism. Once activated, these enzymes transfer phosphate from ATP onto substrate proteins and in doing so affect the properties of substrate molecules. There are four broad classes of protein kinases including serine/threonine kinases, tyrosine kinases, multi-specific or dual-specific kinases, and histidine kinases [Hunter, *et al.*, *Meth.Enzymol. 200*:3-37 (1991)]. In addition to the amino acid residue(s) of the substrate preferentially phosphorylated by the kinase, assignment of an enzyme to a particular class is based on its primary structure, its requirement for regulatory subunits, its requirement for second messengers, and its specific biochemical activity. See Hunter *et al.*, *supra*, and Hanks and Quinn, *Meth. Enzymol., 200*: 38-62 (1991).

Serine/threonine protein kinases have been further divided into families of enzymes based on the mode of regulation of the enzymes and the quaternary structure of the active enzymes [Edelman, *et al.*, *Ann.Rev. Biochem. 56*:567-613 (1987)]. Enzymes within the serine/threonine protein kinase family can differ in the substrates they phosphorylate, the specific phosphorylation sites they recognize, their mode of regulation and their subcellular distribution. Protein kinase A (PKA), for example, phosphorylates target substrates with the recognition/phosphorylation sequence R-R-X-S(P)-Y (SEQ ID NO: 1) [Pearson

and Lemp, *Meth.Enzymol. 200*:62-81 (1991)], where S(P) represents the phosphorylated residue. The activity of PKA is localized by targeting subunits (called anchoring proteins or AKAPs, reviewed in Hubbard and Cohen, *T.I.B.S. 18*:172-177, 1993). Members of the casein kinase I (CKI) family, on the other hand, recognize and phosphorylate serines and threonines near acidic residues in substrate proteins. The genes which encode yeast, rat, bovine and human isoforms of casein kinase I activity are structurally similar and the isoforms exhibit greater than 35%, and frequently greater than 50%, homology (identity) over their catalytic domains when compared to the prototypical *S. cerevisiae* CKI protein, HRR25, and are referred to herein as "HRR25-like" proteins. This degree of identity is significantly greater than the expected 25% found for comparing two randomly chosen protein kinases [Hanks and Quinn, *supra*]. The HRR25 DNA sequence is disclosed in Hoekstra, *et al., Science 253*:1031-1034 (1991); yeast CKI1 and CKI2 DNA sequences in Wang *et al., J. Mol. Biol. Cell, 3*:275-286 (1992) corresponding respectively to yeast sequences YCK2 and YCK1 in Robinson *et al., Proc. Natl. Acad. Sci. (USA) 89*:28-32 (1992); partial bovine CKIα, CKIβ, CKIγ and CKIδ DNA sequences and a full length homolog CKIα DNA sequence in Rowles, *et al., Proc. Natl. Acad. Sci. (USA) 88*:9548-9552 (1991); a full length rat CKIδ DNA sequence in Graves, *et al., J. Biol. Chem., 268*: 6394-6401 (1993); and a partial human erythroid CKIα DNA sequence in Brockman *et al., Proc. Natl. Acad. Sci. (USA) 89*:9454-9458 (1992).

The *S. cerevisiae* protein kinase HRR25 is one of the more extensively characterized isoforms of the CKI family [Hoekstra, *supra*]. Mutations in the HRR25 gene result in a variety of defects that include cell cycle delays, the inability to properly repair DNA strand breaks and characteristic morphological changes. The nature of these defects implies that HRR25 and other CKI isoforms play a significant role in cellular growth.

The importance of protein phosphorylation and protein kinases in health and disease states is evident in cases where expression of a particular

kinase has gone awry; for example, chronic myelogenous leukemia arises from a translocation that places the breakpoint cluster region (BCR) gene next to the ABL tyrosine kinase gene, resulting in a fusion protein comprising the activated protein kinase [see review, Bishop, *et al.*, *Cell 64*:235-288 (1991)]. In addition, many oncogenes, such as Mos [Watson, *et al.*, *Proc.Natl.Acad.Sci.(USA) 79*:4078-4082 (1982)], Src [Anderson, *et al.*, *Mol.Cell.Biol. 5*:1122-1129 (1985)] and Raf [Bonner, *et al.*, *Nucl.Acids Res. 14*:1009-1015 (1986)] are protein kinases.

Most protein kinases phosphorylate a variety of substrates *in vivo* allowing diversity in responses to physiological stimuli [reviewed in Edelman, *et al.*, *supra*]. However, the broader substrate specificity seen for many protein kinases *in vitro*, including activity towards non-physiological substrates, indicates that cellular mechanisms to control the specificity of these enzymes must exist *in vivo*. Understanding the regulatory mechanisms that govern these kinases and the specific role of the kinases in health and disease states requires the identification of substrates, regulatory proteins, and localizing/targeting proteins that interact with the kinases.

There thus exists a need in the art to identify proteins which interact with members of the casein kinase I family of enzymes and to characterize the interacting proteins in terms of their amino acid and encoding DNA sequences. Such information would provide for the large scale production of the proteins, allow for identification of cells which produce the kinases naturally and permit production of antibodies specifically reactive with the kinases. Moreover, elucidation of the substrates, regulation, and localization of these protein kinases would contribute to an understanding of the control of normal and malignant cell growth and provide information essential for the development of therapeutic agents useful for intervention in abnormal and/or malignant cell growth.

SUMMARY OF THE INVENTION

In one of its aspects, the present invention provides methods for identifying proteins, designated TIH proteins, that interact with CKI isoforms [*i.e.*, *S. cerevisiae* HRR25 casein kinase I and HRR25-like protein kinases having at least 35% amino acid homology to HRR25 within the catalytic domain] and for isolating polynucleotides encoding the TIH proteins. A presently preferred method comprises the steps of: a) transforming or transfecting appropriate host cells with a DNA construct comprising a reporter gene under the control of a promoter regulated by a transcription factor having a DNA-binding domain and an activating domain; b) expressing in the host cells a first hybrid DNA sequence encoding a first fusion of part or all of a CKI isoform and either the DNA-binding domain or the activating domain of the transcription factor; c) expressing in the host cells a library of second hybrid DNA sequences encoding second fusions of part or all of putative CKI isoform-binding proteins and either the DNA-binding domain or DNA activating domain of the transcription factor which is not incorporated in the first fusion; d) detecting binding of CKI isoform-binding proteins to the CKI isoform in a particular host cell by detecting the production of reporter gene product in the host cell; and e) isolating second hybrid DNA sequences encoding CKI isoform-binding protein from the particular host cell. Variations of the method altering the order in which the CKI isoforms and putative CKI isoform-binding proteins are fused to transcription factor domains, *i.e.*, at the amino terminal or carboxy terminal ends of the transcription factor domains, are contemplated. In a preferred version of the method, the promoter is the *lexA* promoter, the DNA-binding domain is the *lexA* DNA-binding domain, the activating domain is the GAL4 transactivation domain, the reporter gene is the *lacZ* gene and the host cell is a yeast host cell.

Variations of the method permit identification of either small molecules which inhibit the interaction between a CKI isoform and a CKI-interacting protein. A preferred method to identify small molecule inhibitors

comprises the steps of: a) transforming or transfecting appropriate host cells with a DNA construct comprising a reporter gene under the control of a promoter regulated by a transcription factor having a DNA-binding domain and an activating domain; b) expressing in the host cells a first hybrid DNA sequence encoding a first fusion of part or all of a CKI isoform and either the DNA-binding domain or the activating domain of the transcription factor; c) expressing in the host cells a second hybrid DNA sequence encoding second fusion of part or all of a known CKI isoform-binding protein and either the DNA-binding domain or DNA activating domain of the transcription factor which is not incorporated in the first fusion; d) contacting the cells with a putative inhibitor compound; and e) identifying modulating compounds as those compounds altering production of the reporter gene product in comparison to production of the reporter gene product in the absence of the modulating compound.

An alternative identification method contemplated by the invention for detecting proteins which bind to a CKI isoform comprises the steps of: a) transforming or transfecting appropriate host cells with a hybrid DNA sequence encoding a fusion between a putative CKI isoform-binding protein and a ligand capable of high affinity binding to a specific counterreceptor; b) expressing the hybrid DNA sequence in the host cells under appropriate conditions; c) immobilizing fusion protein expressed by the host cells by exposing the fusion protein to the specific counterreceptor in immobilized form; d) contacting a CKI isoform with the immobilized fusion protein; and e) detecting the CKI isoform bound to the fusion protein using a reagent specific for the CKI isoform. Presently preferred ligands/counterreceptor combinations for practice of the method are glutathione-S-transferase/glutathione, hemagglutinin/hemagglutinin-specific antibody, polyhistidine/nickel and maltose-binding protein/amylose.

The present invention also provides novel, purified and isolated polynucleotides (*e.g.*, DNA sequences and RNA transcripts, both sense and antisense strands) encoding the TIH proteins and variants thereof (*i.e.*, deletion,

addition or substitution analogs) which possess CKI and/or HRR25-binding properties inherent to the TIH proteins. Preferred DNA molecules of the invention include cDNA, genomic DNA and wholly or partially chemically synthesized DNA molecules. Presently preferred polynucleotides are the DNA molecules set forth in SEQ ID NOS: 2 (TIH1), 4 (TIH2), and 6 (TIH3), encoding the polypeptides of SEQ ID NOS: 3 (TIH1), 5 (TIH2), and 7 (TIH3), respectively. Also provided are recombinant plasmid and viral DNA constructs (expression constructs) which comprise TIH polypeptide-encoding sequences operatively linked to a homologous or heterologous transcriptional regulatory element or elements.

As another aspect of the invention, prokaryotic or eukaryotic host cells transformed or transfected with DNA sequences of the invention are provided which express TIH polypeptides or variants thereof. Host cells of the invention are particularly useful for large scale production of TIH polypeptides, which can be isolated from the host cells or the medium in which the host cells are grown.

Also provided by the present invention are purified and isolated TIH polypeptides, fragments and variants thereof. Preferred TIH polypeptides are as set forth in SEQ ID NOS: 3 (TIH1), 5 (TIH2), and 7 (TIH3). Novel TIH and TIH variant products of the invention may be obtained as isolates from natural sources, but are preferably produced by recombinant procedures involving host cells of the invention. Post-translational processing variants of TIH polypeptides may be generated by varying the host cell selected for recombinant production and/or post-isolation processing. Variant TIH polypeptides of the invention may comprise analogs wherein one or more of the amino acids are deleted or replaced: (1) without loss, and preferably with enhancement, of biological properties or biochemical characteristics specific for TIH polypeptides or (2) with specific disablement of a characteristic protein/protein interaction.

Also comprehended by the invention are antibody substances (*e.g.*, monoclonal and polyclonal antibodies, single chain antibodies, chimeric antibodies, CDR-grafted antibodies and the like) which are specifically immunoreactive with TIH polypeptides. Antibody substances are useful, for example, for purification of TIH polypeptides and for isolation, via immunological expression screening, of homologous and heterologous species polynucleotides encoding TIH polypeptides. Hybridoma cell lines which produce antibodies specific for TIH polypeptides are also comprehended by the invention. Techniques for producing hybridomas which secrete monoclonal antibodies are well known in the art. Hybridoma cell lines may be generated after immunizing an animal with purified TIH polypeptides or variants thereof.

The scientific value of the information contributed through the disclosure of DNA and amino acids sequences of the present invention is manifest. As one series of examples, knowledge of the genomic DNA sequences which encode yeast TIH polypeptides permits the screening of a cDNA or genomic DNA of other species to detect homologs of the yeast polypeptides. Screening procedures, including DNA/DNA and/or DNA/RNA hybridization and PCR amplification are standard in the art and may be utilized to isolate heterologous species counterparts of the yeast TIH polypeptides, as well as to determine cell types which express these homologs.

DNA and amino acid sequences of the invention also make possible the analysis of TIH epitopes which actively participate in kinase/protein interactions as well as epitopes which may regulate such interactions. Development of agents specific for these epitopes (*e.g.*, antibodies, peptides or small molecules) which prevent, inhibit, or mimic protein kinase-protein substrate interaction, protein kinase-regulatory subunit interaction, and/or protein kinase-protein localization molecule interaction are contemplated by the invention. Therapeutic compositions comprising the agents are expected to be useful in

modulating the CKI/TIH protein interactions involved in cell growth in health and disease states, for example, cancer and virus-related pathologies.

BRIEF DESCRIPTION OF THE DRAWING

Numerous other aspects and advantages of the present invention will be apparent upon consideration of the following detailed description thereof, reference being made to the drawing wherein:

Figure 1 is a Western blot demonstrating the association of *S. cerevisiae* HRR25 casein kinase I with affinity-purified TIH2.

Figure 2 is an amino acid sequence comparison between TIH1 and enzymes known to participate in removal of aberrant nucleotides.

DETAILED DESCRIPTION

The present invention generally relates to methods for identifying proteins that interact with CKI isoforms and is illustrated by the following examples relating to the isolation and characterization of genes encoding TIH polypeptides. More particularly, Example 1 addresses isolation of DNA sequences encoding TIH polypeptides from a yeast genomic library utilizing a dihybrid screening technique. Example 2 relates to analysis of the interaction between TIH polypeptides and various yeast CKI isoforms. Example 3 addresses interaction between a yeast CKI isoform, including mutants and fragments thereof, and kinesins. Example 4 describes analysis of the interaction between TIH polypeptides and human CKI isoforms. Example 5 addresses isolation of full length genomic DNA sequences which encode TIH polypeptides of the invention. Example 6 describes construction of a TIH knock-out mutant in yeast. Example 7 addresses analysis of *S. cerevisiae* HRR25/TIH polypeptides interactions utilizing affinity purification and Western blotting techniques. Example 8 provides a comparison at the amino acid level between TIH1 and enzymes

identified as participating in degradation of oxidatively damaged nucleotides, thus enhancing fidelity of replication.

Example 1

Cellular components that interact with CKI isoforms were identified by a dihybrid screening method that reconstitutes a transcriptional transactivator in yeast. [A similar "two-hybrid" assay was originally described in Fields and Song, *Nature, 340*: 245-246 (1989) and more recently in Yang *et al., Science 257*:681-682 (1992) and Vojtek *et al., Cell, 74*: 205-214 (1993).] In the assay, "bait" components (*i.e.*, CKI isoforms) are fused to the DNA binding domain of a transcription factor (*e.g.*, the *lex*A protein) and "prey" components (*i.e.*, putative CKI interacting proteins) are fused to the transactivation domain of the transcription factor (*e.g.*, GAL4). Recombinant DNA constructs encoding the fusion proteins are expressed in a host cell that contains a reporter gene fused to promoter regulatory elements (*e.g.* a *lexA* DNA binding site) recognized by the transcription factor. Binding of a prey fusion protein to a bait fusion protein brings together the GAL4 transactivation domain and the *lexA* DNA binding domain allowing interaction of the complex with the *lexA* DNA binding site that is located next to the β-galactosidase reporter gene, thus reconstituting transcriptional transactivation and producing β-galactosidase activity. In variations of the method, the "prey" component can be fused to the DNA binding domain of GAL4 and the "bait" components detected and analyzed by fusion to the transactivation domain of GAL4. Likewise, variations of this method could alter the order in which "bait" and "prey" components are fused to transcription factor domains, *i.e.*, "bait" and "prey" components can be fused at the amino terminal or carboxy terminal ends of the transcription factor domains.

To identify genes encoding proteins that interact with *S. cerevisiae* HRR25 CKI protein kinase, a plasmid library encoding fusions between the yeast GAL4 activation domain and *S. cerevisiae* genomic fragments ("prey"

components) was screened for interaction with a DNA binding domain hybrid that contained the *E. coli lexA* gene fused to HRR25 ("bait" component). The fusions were constructed in plasmid pBTM116 (gift from Bartell and Fields, SUNY) which contains the yeast TRP1 gene, a 2μ origin of replication, and a yeast ADHI promoter driving expression of the *E. coli lex*A DNA binding domain (amino acids 1 to 202).

Plasmid pBTM116::HRR25, which contains the *lexA::HRR25* fusion gene, was constructed in several steps. The DNA sequence encoding the initiating methionine and second amino acid of HRR25 was changed to a *Sma*I restriction site by site-directed mutagenesis using a MutaGene mutagenesis kit from BioRad (Richmond, California). The DNA sequence of HRR25 is set out in SEQ ID NO: 8. The oligonucleotide used for the mutagenesis is set forth below, wherein the *Sma*I site is underlined.

5'-CCT ACT CTT AGG CCC GGG TCT TTT TAA TGT ATC C-3'
(SEQ ID NO. 9)

After digestion with *Sma*I, the resulting altered HRR25 gene was ligated into plasmid pBTM116 at the *Sma*I site to create the lexA::HRR25 fusion construct.

Interactions between bait and prey fusion proteins were detected in yeast reporter strain CTY10-5d (genotype=*MATa ade2 trp1-901 leu2-3,112 his 3-200 gal4 gal80 URA3::lexA op-lacZ.*) [Luban, *et al., Cell 73*:1067-1078 (1993)] carrying a *lex*A binding site that directs transcription of *lacZ* . Strain CTY10-5d was first transformed with plasmid pBTM116::HRR25 by lithium acetate-mediated transformation [Ito, *et al., J.Bacteriol. 153*:163-168 (1983)]. The resulting transformants were then transformed with a prey yeast genomic library prepared as GAL4 fusions in the plasmid pGAD [Chien, *et al., Proc.Natl.Acad.Sci (USA) 21*:9578-9582 (1991)] in order to screen the expressed proteins from the library for interaction with HRR25. A total of 500,000 double transformants were assayed for β-galactosidase expression by replica plating onto nitrocellulose

filters, lysing the replicated colonies by quick-freezing the filters in liquid nitrogen, and incubating the lysed colonies with the blue chromogenic substrate 5-bromo-4-chloro-3-indolyl-β-D-galactoside (X-gal). β-galactosidase activity was measured using Z buffer (0.06 M Na_2HPO_4, 0.04 M NaH_2PO_4, 0.01 M KCl, 0.001 M $MgSO_4$, 0.05 M β-mercaptoethanol) containing X-gal at a concentration of 0.002% [Guarente, *Meth. Enzymol. 101*:181-191 (1983)]. Reactions were terminated by floating the filters on 1M Na_2CO_3 and positive colonies were identified by their dark blue color.

Library fusion plasmids (prey constructs) that conferred blue color to the reporter strain co-dependent upon the presence of the HRR25/DNA binding domain fusion protein partner (bait construct) were identified. The sequence adjacent to the fusion site in each library plasmid was determined by extending DNA sequence from the GAL4 region. The sequencing primer utilized is set forth below.

5'-GGA ATC ACT ACA GGG ATG-3' (SEQ ID NO. 10)

DNA sequence was obtained using a Sequenase version II kit (US Biochemicals, Cleveland, Ohio) or by automated DNA sequencing with an ABI373A sequencer (Applied Biosystems, Foster City, California).

Four library clones were identified and the proteins they encoded are designated herein as TIH proteins 1 through 4 for Targets Interacting with HRR25-like protein kinase isoforms. The TIH1 portion of the TIH1 clone insert corresponds to nucleotides 1528 to 2580 of SEQ ID NO: 2; the TIH2 portion of the TIH2 clone insert corresponds to nucleotides 2611 to 4053 of SEQ ID NO: 4; the TIH3 portion of the TIH3 clone insert corresponds to nucleotides 248 to 696 of SEQ ID NO: 6; and the TIH4 portion of the TIH4 clone insert is set out in SEQ ID NO: 11 and corresponds to nucleotides 1763 to 2305 of SEQ ID NO: 28. Based on DNA sequence analysis of the TIH genes, it was determined that TIH1 and TIH3 were novel sequences that were not representative of any protein motif present in the GenBank database (July 8, 1993). TIH2 sequences were

identified in the database as similar to a yeast open reading frame having no identified function. (GenBank Accession No. Z23261, open reading frame YBL0506) TIH4 represented a fusion protein between GAL4 and the carboxy-terminal portion of the kinesin-like protein KIP2. KIP2 has a highly conserved region which contains a kinesin-like microtubule-based motor domain [Roof *et al.*, *J. Cell. Biol. 118*(1):95-108 (1992)]. The isolation of corresponding full length genomic clones for TIH1 through TIH3 is described in Example 5.

Example 2

To investigate the specificity of interaction and regions of interaction between CKI isoforms and the TIH proteins, bait constructs comprising mutant or fragment HRR25 isoforms or other yeast (NUF1 and Hhp1) CKI isoforms fused to the lexA DNA binding domain were examined for transcription transactivation potential in the dihybrid assay.

Plasmid Constructions

To construct a plasmid containing a catalytically-inactive HRR25 protein kinase, HRR25 DNA encoding a lysine to arginine mutation at residue 38 (the ATP binding site) of HRR25 [DeMaggio *et al.*, *Proc. Natl. Acad. Sci. (USA) 89*(15): 7008-7012 (1992)] was generated by standard site-directed mutagenesis techniques. The resulting DNA was then amplified by a PCR reaction which inserted a *Sma*I restriction site (underlined in SEQ ID NO. 12) before the HRR25 ATG using a mutagenic oligonucleotide:

5′-CCT TCC TAC TCT TAA GCC CGG GCC GCA GGA ATT CG-3′ (SEQ ID NO 12),

and the downstream oligonucleotide which inserted a *Bam*HI site (underlined):

5′-AGC AAT ATA GGA TCC TTA CAA CCA AAT TGA-3′ (SEQ ID NO: 13).

Reactions included 200mM Tris-Hcl (pH 8.2), 100mM KCl, 60 mM $(NH_4)_2SO_4$, 15mM $MgCl_2$, 1% Triton X-100, 0.5 μM primer, 100 ng template, 200 μM dNTP and 2.5 units polymerase. The reactions were performed for 30 cycles. Reactions were started with a 4 minute treatment at 94°C and all cycles were 1 minute at 94°C for denaturing, 2 minutes at 50°C for annealing, and 4 minutes at 72°C for extension. The resulting amplification product was digested with *Sma*I and ligated at the *Sma*I site of pBTM116 to produce the plasmid designated pBTM116::HRR25K→R encoding *lex*A sequences fused 5′ to HRR25 sequences.

To construct a pBTM116 plasmid encoding a catalytic domain fragment of HRR25, two rounds of site-directed mutagenesis were performed to introduce a *Sma*I site in place of the initiating ATG and second codon of HRR25 DNA and a *Bam*HI site at nucleotide 1161 (refer to SEQ ID NO. 8) or amino acid 397 of HRR25. The mutagenic oligonucleotide used to introduce the 5′ *Sma*I restriction site (underlined) was:

5′-CCT ACT CTT AAG CCC GGG TCT TTT TAA TGT ATC C-3′

(SEQ ID NO. 14),

and the oligonucleotide used to create the 3′, or downstream, *Bam*HI site (underlined) at residue 397 was:

5′-GTC TCA AGT TTT GGG ATC CTT AAT CTA GTG CG-3′

(SEQ ID NO. 15).

The resulting product was digested with *Sma*I-*Bam*HI and the fragment encoding the HRR25 catalytic domain (corresponding to nucleotides 2 to 1168 of SEQ ID NO: 8) was subcloned into plasmid pBTM116 linearized with the same enzymes to produce the plasmid designated pBTM116::Kinase domain encoding *lex*A sequences fused 5′ to HRR25 sequences.

To construct a pBTM116 plasmid containing the non-catalytic domain fragment of HRR25, a *Sma*I site (underlined) was introduced at nucleotide 885 (amino acid 295) using site-directed mutagenesis with the following oligonucleotide:

5'-CAC CAT CGC CCC CGG GTA ACG CAA CAT TGT CC-3'
(SEQ ID NO: 16).

The resulting product was digested with *Sma*I and *Bam*HI and the fragment encoding the HRR25 non-catalytic domain (corresponding to nucleotides 885 to 1485 of SEQ ID NO: 8) was subcloned into plasmid pBTM116 linearized with the same enzymes to produce the plasmid designated pBTM116::Non-catalytic encoding *lex*A sequences fused 5' to HRR25 sequences.

To construct a fusion with the *S. cerevisiae* NUF1 isoform of CKI in plasmid pBTM116, a *Sma*I site (underlined) was introduced by site-directed mutagenesis in place of the initiating ATG and second codon of NUF1 DNA (SEQ ID NO: 17) using the oligonucleotide:
5'-TGA AGA TCG TTG GCC CGG GTT TCC TTA TCG TCC-3'
(SEQ ID NO. 18).

The resulting product was digested with *Sma*I and *Bam*HI and the NUF1 fragment was ligated into pBTM116 linearized with the same enzymes sites to produce the plasmid designated pBTM116::NUF1 encoding *lex*A sequences fused 5' to NUF1 sequences.

To construct a fusion with the *S. pombe* Hhp1 isoform of CKI in plasmid pBTM116, a *Sma*I site (underlined) was introduced by site-directed mutagenesis in place of the initiating ATG and second codon of Hhp1 DNA (SEQ ID NO: 19) using the oligonucleotide:
5'-GGG TTA TAA TAT TAT CCC GGG TTT GGA CCT CCG G-3'
(SEQ ID NO. 20).

The resulting product was digested with *Sma*I and *Bam*HI and the HhpI fragment was ligated into pBTM116 linearized with the same enzymes to produce plasmid pBTM116::Hhp1 encoding *lex*A sequences fused 5' to Hhp1 sequences.

Assays

To measure protein/protein interaction levels between wild-type and mutant CKI isoforms and TIH proteins of the invention, standard yeast mating techniques were used to generate yeast strains containing all pairwise combinations of the isoforms and TIH proteins. All CKI isoform-encoding pBTM116-based plasmids were transformed into yeast by lithium acetate-mediated transformation methods and transformants were selected on SD-tryptophan medium (Bio101, La Jolla, CA). The yeast strain CTY10-5d used for pBTM116-based transformations was mating type α. All TIH protein-encoding pGAD-based plasmids described in Example 1 were transformed using the lithium acetate method into yeast and transformants were selected on SD-leucine medium. The yeast strain used for pGAD-based transformations was mating type a. This MATa strain is isogeneic to CTY10-5d and was constructed by introducing the *HO* gene using plasmid pGALHO [Jenson and Herskowitz, *Meth.Enzymol. 194*:132-146 (1991)] in lithium acetate-mediated transformation, inducing the *HO* gene with galactose to cause a mating-type interconversion, and growing the strain non-selectively to isolate a derivative that had switched mating type.

To construct pairwise combinations between pBTM116-based plasmids and pGAD-based plasmids, yeast strains of opposite mating types were replica plated in a crossed pattern on YEPD medium (Bio101) and were allowed to mate for 18 hours. Diploid cells were selected by a second replica plating onto SD-leucine, -tryptophan medium to select for cells that contained both pBTM116-type and pGAD-type plasmids. The isolated diploids were grown in liquid SD-leucine, -tryptophan medium to a cell density of 2×10^7 cells/ml and the level of interaction of the kinase and interacting protein, as determined by beta-galactosidase activity, was determined from cells that were lysed by adding 3 drops of chloroform and 50 μl of 0.1% SDS to 2×10^6 cells suspended in 0.1 ml of Z buffer and subsequently adding 0.2 ml of the chromogenic substrate *o*-nitrophenyl-β-D-galactoside. β-galactosidase assays were terminated by adding

0.5 ml of 1M Na_2CO_3 and activity was measured by reading absorbance at 420 nm using a Milton Roy spectrophotometer (Rochester, New York). In this assay, the degree of protein/protein interaction is directly proportional to the level of β-galactosidase activity. The relative β-galactosidase activity measurements obtained are given in Table 1, wherein a value of <5 indicates that the level of β-galactosidase activity was not greater than background and a value of 10 indicates a easily detectable level of activity. Values were normalized to vector alone controls.

Table 1

Yeast CKI/TIH Protein Interactions

PLASMID CONSTRUCTS ASSAYED	pGAD ::TIH1	pGAD ::TIH2	pGAD ::TIH3
pBTM116	<5	<5	<5
pBTM116:HRR25	850	650	100
pBTM116::HRR25 K→R	100	150	30
pBTM116::Kinase Domain	820	160	130
pBTM116::Non-catalytic	<5	<5	<5
pBTM116::NUF1	<5	<5	10
pBTM116::Hhp1	<5	20	450

The results show significant interaction between HRR25 protein kinase and the TIH genes. Furthermore, the interaction appeared to require an active protein kinase; the region of HRR25 that interacted with the TIH proteins is localized to the protein kinase domain of HRR25. TIH proteins of the invention also interacted with other CKI isoforms. For example, TIH3 interacted with NUF1, and TIH2 and TIH3 interacted with HhpI.

Example 3

Because HRR25 mutants (hrr25) show chromosome segregation defects and because kinesins are involved in chromosome segregation, the interaction of several different kinesins with the CKI bait fusions described in Example 2 was examined. To date, the kinesin gene family in yeast includes proteins designated KIP1 (Roof *et al. supra*), KIP2 (Roof *et al., supra*), CIN8 [Hoyt *et al., J. Cell. Biol. 11*(1): 109-120 (1992)] and KAR3 [Meluh *et al., Cell 60*(6): 1029-1041 (1990)]. To construct the prey kinesin fusion plasmids, genomic clones of KIP1, KIP2, CIN8, and KAR3 were first isolated and then subcloned into plasmid pGAD which contains the transactivating domain of GAL4. Interactions of the CKI bait fusions with the TIH4 prey fusion (pGAD::TIH4) described in Example 1 were examined concurrently.

Plasmid Construction

KIP1 sequences were amplified from *S. cerevisiae* genomic DNA using the following two primers:

5'-TCC CTC TCT AGA TAT GGC GAG ATA GTT A-3' (SEQ ID NO: 21) and

5'-GTT TAC ACT CGA GGC ATA TAG TGA TAC A-3' (SEQ ID NO: 22).

The amplified fragment was labelled with ^{32}P by random primed labelling (Boehringer Mannheim, Indianapolis, Indiana) and used to screen a yeast genomic library constructed in the plasmid pRS200 (ATCC 77165) by colony hybridization. Hybridizations were performed at 65°C for 18 hours in 6X SSPE (20X SSPE is 175.3 g/l NaCl, 27.6 g/l NaH2PO4.H2), 7.4 g.l EDTA, pH7.4, 100 μg/ml salmon sperm carrier DNA, 5X Denhardts Reagent (50X Denhardts is 5% ficoll, 5% polyvinyl pyrolidone, 5% bovine serum albumin), 0.1% SDS, and 5% sodium dextran sulfate. Filters were washed four times in 0.1X SSPE, 1% SDS. Each wash was at 65°C for 30 minutes. Two rounds of site-directed mutagenesis were then performed as described in Example 2 to introduce *Bam*HI sites at the start and end of KIP1 coding sequences (SEQ ID NO: 23). Mutagenesis was performed using a Muta-gene Mutagenesis Kit, Version 2

(BioRad). The oligonucleotide for introducing a *Bam*HI site (underlined) in place of the KIP1 ATG and second codon was:

5′-GAT AGT TAA GGA TCC ATG GCT CGT TCT TCC TTG CCC AAC CGC-3′ (SEQ ID NO: 24),

and the oligonucleotide encoding a stop codon (double underlined) and *Bam*HI site (underlined) was:

5′-AAA CTT CAT CAA TGC GGC CGC TAA GGG GAT CCA GCC ATT GTA AAT-3′ (SEQ ID NO: 25).

The resulting KIP1 product was digested with *Bam*HI and cloned into pGAD immediately downstream of GAL4 sequences and the plasmid was called pGAD::KIP1.

KIP2 sequences were amplified from *S. cerevisiae* genomic DNA using the following two primers:

5′-TTT CCT TGT TTA TCC TTT TCC AA-3′ (SEQ ID NO: 26) and

5′-GAT CAC TTC GGA TCC GTC ACA CCC AGT TAG-3′ (SEQ ID NO: 27).

The amplified fragment was labelled with ^{32}P by random primed labelling and used to screen a yeast genomic library constructed in the plasmid YCp50 (ATCC 37415) by colony hybridization. Hybridizations and washes were as described above for KIP1. Two rounds of site-directed mutagenesis were performed to introduce *Bam*HI sites at the start and end of KIP2 coding sequences (SEQ ID NO: 28). The oligonucleotide for introducing a *Bam*HI site (underlined) in place of the KIP2 ATG and second codon was:

5′-ACC ATA ATA CCA GGA TCC ATG ATT CAA AAA-3′ (SEQ ID NO: 29)

and the oligonucleotide encoding a *Bam*HI site (underlined) was:

5′-CCT GTC GTG GAT AGC GGC CGC TAG GAT CCT GAG GGT CCC AGA-3′ (SEQ ID NO: 30).

The resulting KIP2 product was digested with *Bam*HI and cloned into pGAD immediately downstream of GAL4 sequences and the plasmid was called pGAD::KIP2.

CIN8 sequences were amplified from *S. cerevisiae* genomic DNA using the following two primers:

5'-ACA TCA TCT AGA GAC TTC CTT TGT GAC C-3' (SEQ ID NO: 31) and

5'-TAT ATA ATC GAT TGA AAG GCA ATA TC-3' (SEQ ID NO: 32).

The amplified fragment was labelled with ^{32}P by random primed labelling and used to screen a yeast genomic library constructed in the plasmid pRS200 (ATCC 77165) by colony hybridization. Hybridizations and washes were as described above for KIP1. Two rounds of site-directed mutagenesis were performed to introduce *Bam*HI sites at the start and end of CIN8 coding sequences (SEQ ID NO: 33). The oligonucleotide utilized for introducing a *Bam*HI site (underlined) in place of the CIN8 ATG and second codon was:

5'-CGG GTG TAG GAT CCA TGG TAT GGC CAG AAA GTA ACG-3' (SEQ ID NO: 34)

and the downstream oligonucleotide encoding a *Bam*HI site (underlined) and a stop codon (double underlined) was:

5'-GTG GAC AAT GGC GGC CGC AGA AAA AGG ATC CAG ATT GAA TAG TTG ATA TTG CC-3' (SEQ ID NO: 35).

The resulting CIN8 product was digested with *Bam*HI and cloned into pGAD immediately downstream of GAL4 sequences and the plasmid was called pGAD::CIN8.

KAR3 was amplified from *S. cerevisiae* genomic DNA using the following two primers:

5'-GAA TAT TCT AGA ACA ACT ATC AGG AGT C-3' (SEQ ID NO: 36) and

5'-TTG TCA CTC GAG TGA AAA AGA CCA G-3' (SEQ ID NO: 37).

The amplified fragment was labelled with ^{32}P by random primed labelling and used to screen a yeast genomic library constructed in the plasmid pRS200 (ATCC 77165) by colony hybridization. Hybridizations and washes were as described above for KIP1. Two rounds of site-directed mutagenesis were performed to introduce *Bam*HI sites at the start and end of KAR3 coding sequences (SEQ ID

NO: 38). The oligonucleotide for introducing a *Bam*HI site (underlined) in place of the KAR3 ATG and second codon was:

5′-GAT AGT TAA GGA TCC ATG GCT CGT TCT TCC TTG CCC AAC CGC-3′ (SEQ ID NO: 39)

and the oligonucleotide encoding a *Bam*HI site (underlined) and a stop codon (double underlined) was:

5′-AAA CTT CAT CAA TGC GGC CGC TAA GGG GAT CCA GCC ATT GTA AAT-3′ (SEQ ID NO: 40).

The resulting KAR3 product was digested with *Bam*HI and cloned into pGAD immediately downstream of GAL4 sequences and the plasmid was called pGAD::KAR3.

The prey plasmids were transformed into yeast by lithium acetate-mediated transformation and the transformants were mated to CKI isoform-encoding yeast strains as described in Example 2. β-galactosidase activity of CKI isoform/TIH-containing strains was determined from cells that were lysed by adding 3 drops of chloroform and 50 μl of 0.1% SDS to 2 x 10^6 cells suspended in 0.1 ml of Z buffer and subsequently adding 0.2 ml of the chromogenic substrate *o*-nitrophenyl-β-D-galactoside. β-galactosidase assays were terminated by adding 0.5 ml of 1M Na_2CO_3 and activity was measured by reading absorbance at 420 nm using a Milton Roy spectrophotometer (Rochester, New York). In this assay, the degree of protein/protein interaction is directly proportional to the level of β-galactosidase activity. The results of the assay are presented as units of β-galactosidase activity in Table 2.

Table 2

β-Galactosidase Activity Resulting From CKI Isoform/Kinesin Interaction

	pGAD:: KIP1	pGAD:: KIP2	pGAD:: TIH4	pGAD:: KAR3	pGAD:: CIN8
pBTM116 ::HRR25	16	10	70	15	5
pBTM116: :HRR25 K→R	55	16	66	75	28
pBTM116 ::Non-Catalytic	70	<0.1	<0.1	60	<0.1

The results indicate that HRR25 can interact with all four yeast kinesins and TIH4. Kinesins KIP2 and CIN8 interact with the catalytic domain of HRR25 while kinesins KIP1 and KAR3 interact with kinase-inactive HRR25 and with the non-catalytic domain of HRR25, suggesting that kinase/substrate interaction progresses through strong binding to enzymatic activity. In addition, the results show that HRR25 interacts with the carboxy-terminal portion of TIH4 or, because TIH4 corresponds to KIP2, KIP2.

Example 4

Assays were also performed to determine whether human CKI isoforms would interact with the TIH proteins of the invention. Two human CKI isoforms, CKIα3 (CKIα3Hu) and CKIδ (CKIδHu), were selected for this analysis. The human CKI genes were fused to the GAL4 DNA binding domain previously inserted into plasmid pAS [Durfee, *et al.*, *Genes and Development* 7:555-569 (1993)] to produce pAS::CKIα3 and pAS::CKIδ.

Specifically, the CKIα3Hu isoform-encoding DNA (SEQ ID NO: 41) was subjected to site-directed mutagenesis using the mutagenic oligonucleotide:

5′-CTT CGT CTC TCA CAT ATG GGC GAG TAG CAG CGG C-3′

(SEQ ID NO. 42)

to create *Nde*I site (underlined) in the place of the CKIα 3Hu initiating methionine and second codon, and the resulting DNA was digested with *Nde*I and ligated into plasmid pAS at a *Nde*I site located immediately downstream of GAL4 sequences.

CKIδHu DNA (SEQ ID NO: 43) was introduced into pAS by amplifying the CKIδ cDNA with mutagenic oligonucleotide primers that contained *Bam*HI sites. The oligonucleotides, with *Bam*HI sites underlined, used were:

5′-CGC GGA TCC TAA TGG AGG TGA GAC TCG GG-3′ (SEQ ID NO. 44), replacing the initiating methionine and second codon,

and

5′-CGC GGA TCC GCT CAT CGG TGC ACG ACA GA-3′ (SEQ ID NO. 45).

Reactions included 200mM Tris HCl (pH 8.2), 100mM KCl, 60mM $(NH_4)_2SO_4$, 15 mM $MgCl_2$, 1% Triton X-100, 0.5 μM primer, 100 ng template, 200 μM dNTP and 2.5 units polymerase. The reactions were performed for 30 cycles. Reactions were started at 94°C for 4 minutes and all subsequent cycles were 1 minute at 94°C for denaturing, 2 minutes at 50°C for annealing, and 4 minutes at 72°C for extension. The amplified product was digested with *Bam*HI and ligated into *Bam*HI-digested pAS immediately downstream of GAL4 sequences to create plasmid pAS:CKIδ.

The resulting bait plasmids were transformed into yeast by lithium acetate-mediated transformation and the transformants were mated to TIH-encoding yeast strains as described in Example 2. β-galactosidase activity of CKIα3Hu- or CKIδHu-containing/TIH-containing strains was detected by replica plating cells onto Hybond-$N^{0.45\mu}$ filters (Amersham, Arlington Heights, IL), growing cells on the filters at 30°C for 18 hours, lysing the colonies by freezing

the filters in liquid nitrogen, and incubating the filters on Whatman filter paper soaked in Z buffer containing 0.002% X-gal. Reactions were terminated by soaking the filters in 1M Na_2CO_3 and protein/protein interaction was evaluated by examining for a chromogenic conversion of X-gal to blue by β-galactosidase activity. The results of the assay, as determined by visual screening for development of blue color are presented below in Table 3.

Table 3

β-Galactosidase Activity Resulting From Human CKI/TIH Interaction

PLASMID CONSTRUCTS USED	TIH1	TIH2	TIH3
pAS::CKIα3	-	-	-
pAS::CKIδ	-	+	-

These results indicate that interaction between TIH proteins of the invention and CKI isoforms is not limited to yeast isoforms. CKIδHu interacted with TIH2. Thus, CKI/TIH interactions can be expected to occur between human CKIs and their cognate TIH proteins.

Example 5

Full length genomic clones encoding the yeast TIH1, TIH2, and TIH3 proteins were isolated from a yeast genomic library. To identify genomic clones, radiolabelled PCR fragments were prepared from the pGAD plasmids containing TIH1, TIH2, and TIH3 fusion genes described in Example 1. The sequence of the unidirectional oligonucleotide used to amplify the clones was:
5′-GGA ATC ACT ACA GGG ATG-3′ (SEQ ID NO. 46).
PCR reactions included 200mM Tris HCl (pH 8.2), 100mM KCl, 60mM $(NH_4)_2SO_4$, 15mM $MgCl_2$, 1% Triton X-100, 0.5 μM primer, 100 ng template,

200 μM dNTP and 2.5 units polymerase. The reactions were performed for 30 cycles. The first five cycles contained 50 μCi each ^{32}P-dCTP and ^{32}P-TTP. At the start of the sixth cycle, non-radiolabeled dCTP and dTTP were each added to 200μM final concentration. Reactions were started at 94°C for 4 minutes and all subsequent cycles were performed for 1 minute at 94°C for denaturation, 2 minutes at 50°C for annealing, and 4 minutes at 72°C for extension. The resulting PCR products were then used as probes in colony hybridization screening.

The full length TIH1 genomic clone was isolated from a YCp50 plasmid library (ATCC 37415). The full length TIH2 and TIH3 genomic clones were isolated from a λ genomic library [Riles, *et al.*, *Genetics 134*:81-150 (1993)]. Hybridization for YCp50 library screening were performed at 65°C for 18 hours in 6X SSPE (20X SSPE is 175.3 g/l NaCl, 27.6 g/l NaH_2PO_4.H2), 7.4 g.l EDTA, pH7.4, 100 μg/ml salmon sperm carrier DNA, 5X Denhardts Reagent (50X Denhardts is 5% ficoll, 5% polyvinyl pyrolidone, 5% bovine serum albumin), 0.1% SDS, and 5% sodium dextran sulfate. Filters were washed four times in 0.1X SSPE, 1% SDS. Each wash was at 65°C for 30 minutes. Hybridization conditions for λ library screening were 18 hours at 64°C in 1X HPB (0.5M NaCl, 100mM Na_2HPO_4, 5mM Na_2EDTA), 1% sodium sarkosyl, 100 μg/ml calf thymus DNA. Filters were washed two times for 15 seconds, one time for 15 minutes, and one time for 15 seconds, all at room temperature in 1mM Tris-HCl (pH 8.0). The sequences of TIH1, TIH2, and TIH3 genomic clones were determined by automated DNA sequencing with an ABI 373A sequencer (Applied Biosystems). Nucleotide sequences determined for the full length TIH1, TIH2 and TIH3 genomic clones are set out in SEQ ID NOS: 2, 4, and 6, respectively; the deduced amino acid sequences for TIH1, TIH2, and TIH3 are set out in SEQ ID NOS: 3, 5, and 7, respectively. Database searches confirmed the results from Example 1 that the TIH1 and TIH3 genes encoded novel proteins showing no significant homology to any protein in the GenBank database.

Example 6

To characterize activity of the TIH proteins and to determine if the TIH proteins participate in a HRR25 signalling pathway, a chromosomal TIH1 deletion mutant was constructed by homologous recombination.

Specifically, the TIH1 mutation was constructed by subcloning a 1.7 kb *SalI-Bam*HI fragment that encompasses the genomic TIH1 gene into plasmid pBluescript II SK (Stratagene, La Jolla, CA). The resulting subclone was digested with *Eco*RV and *Pst*I to delete 0.5 kb of the TIH1 gene (nucleotides 1202 to 1635 of SEQ ID NO: 2) and into this region was ligated a 2.2 kb *Sma*I-*Pst*I fragment that contained the *S. cerevisiae* LEU2 gene. Isolated DNA from the resulting plasmid construct was digested with *Bam*HI to linearize the plasmid and 10 μg of this sample were used to transform a diploid yeast strain that is heterozygous for HRR25 (*MAT a/MAT α ade2/ade2 can1/can1 his3-11,15/his3-11,15 leu2-3,112/leu2-3,112 trp1-1/trp1-1 ura3-1/ura3-1 HRR25/hrr25::URA3*) to Leu^+. Transformation was carried out using lithium acetate-mediated procedures and transformants were selected on SD-Leucine medium (Bio101). Yeast transformation with linearized DNA results in homologous recombination and gene replacement [Rothstein, *Meth. Enzymol. 194*:281-301 (1991)]. Stable Leu^+ colonies were replica plated onto sporulation medium (Bio101) and grown at 30°C for five days. Spores were microdissected on YEPD medium (Bio101) using a tetrad dissection apparatus [Sherman and Hicks, *Meth. Enzymol. 194*:21-37 (1991)] and isolated single spores were allowed to germinate and grow into colonies for three days.

Four colony types were detected due to random meiotic segregation of the heterozygous TIH1 and HRR25 mutations present in the strain. The hrr25 deletion mutation in the parent strain was due to a replacement of the HRR25 gene with the yeast URA3 gene and the TIH1 mutation is due to a replacement with LEU2. URA3 and LEU2 confer uracil and leucine prototropy, respectively. The colony types are represented by segregation of the mutations into following

genotypic configurations: (i) wild type cells are HRR25 TIH1; (ii) HRR25 mutants are hrr25::URA3 TIH1; (iii) TIH1 mutants are HRR25 tih1::LEU2; and (iv) HRR25 TIH1 double mutants are hrr25::URA3 tih1::LEU2. Standard physiological analyses of yeast mutant defects were performed [Hoekstra *et al.*, *supra*].

TIH1 deletion mutants exhibited phenotypes identical to mutations in HRR25 including slow growth rate, DNA repair defects, and aberrant cellular morphology, indicating that the TIH proteins participate in the same pathway as HRR25 or in pathways having similar effects. Furthermore, tih1 hrr25 double mutants were inviable.

Example 7

To confirm the dihybrid screen analysis of interaction between CKI protein kinases and TIH proteins, a biochemical method was developed to detect the interaction. This method was based on affinity purification of one component in the interaction, followed by Western blotting to detect the presence of the interacting component in the affinity purified mixture. The TIH2 gene was used to construct a TIH2/glutathione-S-transferase (GST) fusion protein which could be affinity purified with glutathione agarose (Pharmacia, Uppsala, Sweden) Other useful ligand/counterreceptor combinations include, for example, influence virus hemagglutinin [Field *et al.*, *Mol. Cell Biol.* *8*(5): 2159-2165 (1988)]/hemagglutinin-specificantibody (Berkeley Antibody Company, Richmond, CA), polyhistidine/nickel affinity chromatography (Novagen, Madison, WI), and maltose-binding protein/amylose chromatography (New England Biolabs, Beverly, Massachusetts).

To construct the GST::TIH2 fusion protein, the 5′ and 3′ termini of the TIH2 gene were modified by DNA amplification-based mutagenesis procedures. The amplifying oligonucleotides introduced *Xba*I and *Hind*III sites

for ease in subcloning. The oligonucleotides, with restriction sites underlined, used for amplification were:

5´-ATT CTA GAC ATG GAG ACC AGT TCT TTT GAG-3´

(SEQ ID NO. 47) and,

5´-TGG AAG CTT ATA TTA CCA TAG ATT CTT CTT G-3´

(SEQ ID NO. 48).

Reactions included 200mM Tris-HCl (pH 8.2), 100mM KCl, 60 mM $(NH_4)_2SO_4$, 15mM $MgCl_2$, 1% Triton-X-100, 0.5 μM primer, 100 ng template, 200 μM dNTP and 2.5 units polymerase. The reactions were performed for 30 cycles. Reactions were started at 94°C for 4 minutes and all subsequent cycles were 1 minute at 94°C for denaturation, 2 minutes at 50°C for annealing, and 4 minutes at 72°C for extension.

The resulting amplified product was digested with *Xba*I and *Hind*III and the fragment was subcloned into the GST-containing plasmid pGEXKG, which contained a galactose-inducible GST gene, to create pGEXKG::TIH2. This plasmid contains, in addition to the GST sequences fused immediately upstream of TIH2 sequences, URA3 and LEU2 selectable markers for yeast transformation. Plasmid pGEXKG::TIH2 was then transformed by lithium acetate-mediated transformation into yeast strain W303 [Wallis, *et al.*, *Cell 58*:409-419 (1989)] and Ura^+ transformants were selected on SD-URA medium (Bio101). To isolate the GST::TIH2 fusion protein, 100 ml SD-URA broth was inoculated with the transformed yeast and grown to a density of 1 x 10^7 cells/ml in the presence of galactose. The cells were then pelleted by centrifugation, washed in lysis buffer [10mM sodium phosphate pH 7.2, 150mM NaCl, 1% Nonidet P-40, 1% Trasylol (Miles), 1mM dithiothreitol, 1mM benzamidine, 1mM phenylmethyl sulphonyl fluoride, 5mM EDTA, 1 μg/ml pepstatin, 2 μg/ml pepstatin A, 1 μg/ml leupeptin, 100mM sodium vanadate, and 50mM NaF], resuspended in 1 ml lysis buffer, and lysed by vortexing for 5 minutes with 10 g of glass beads. The crude lysate was clarified by centrifugation at 100,000 x g for 30 minutes. Fifty μl of 50% slurry

glutathione agarose (Pharmacia) was added to the extract and the mixture incubated for 1 hour. The agarose was pelleted by a 10 second spin in an Eppendorf microcentrifuge, the supernate removed, and the agarose-containing pellet washed with phosphate-buffered saline (PBS). The pellet was resuspended in 50 μl of 2X protein gel sample buffer, boiled for 2 minutes, and 12.5 μl was electrophoresed through a 10% polyacrylamide gel. Gel fractionated proteins were transferred by electroblotting to Immobilon-P membranes (Millipore, Bedord, MA) and HRR25 was detected by probing the membrane with a rabbit antibody [DeMaggio *et al., Proc. Natl. Acad. Sci. (USA) 89*: 7008-7012 (1992)] raised to HRR25. The Western blot was developed for immunoreactivity using an alkaline phosphatase-conjugated secondary antibody and colorimetric development (BioRad).

A photograph of the gel is presented in Figure 1, wherein the approximately 58 kD HRR25 protein was detected in association with TIH2 protein.

Example 8

In order to confirm the novelty of the identified TIH1 protein, a data base search of previously reported protein sequences was performed. As shown in Figure 2, wherein portions of the amino acids sequence of TIH1 (amino acids 128 to 161 in SEQ ID NO: 3), human Hum80DP (amino acids 31 to 63) [Sakumi, *et al., J.Biol.Chem. 268*:23524-23530 (1993)], *E.coli* MutT (amino acids 32- to 64) [Akiyama, *et al., Mol.Gen.Genet. 206*:9-16 (1989)], viral C11 (amino acids 122 to 154) [Strayer, *et al., Virol. 185*:585-595 (1991)] and viral VD10 (amino acids 122 to 154) [Strayer, *et al.*, (1991), *supra*)] are respectively set out, sequence comparison indicated that TIH1 contains a signature sequence motif associated with enzymes which actively participate in removal of oxidatively damaged nucleotides from the nucleus, thus increasing the fidelity of DNA replication. Enzymes with this activity have been identified in a wide range of

organisms, including prokaryotes, eukaryotes and viruses [Koonin, *Nucl. Acids Res. 21*:4847 (1993)].

HRR25 enzyme activity has been shown to participate in repair of DNA damaged by radiation, however the role of HRR25 in the repair process has not been determined. The fact that TIH1 has an amino acid sequence similar to that of enzymes capable of degrading damaged indicates that TIH1 is likely to interact with HRR25 in the DNA repair process. Inhibitor compounds which are capable of interfering, or abolishing, the interaction between HRR25 and TIH1 would thus be particularly useful in targeted cancer and antiviral therapy. Delivery of an inhibitor to cancerous or virus-infected cells would increase the rate of replicative mutation in the cells, thus increasing the likelihood of induced cell suicide. In addition, targeted delivery of an inhibitor would selectively confer enhanced sensitivity of cancerous or virus-infected cells to treatment with conventional chemotherapy and/or radiation therapy, thus enhancing the chemotherapy and/or radiotherapy therapeutic index.

While the present invention has been described in terms of specific methods and compositions, it is understood that variations and modifications will occur to those skilled in the art. Therefore, only such limitations as appear in the claims should be placed on the invention.

SEQUENCE LISTING

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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Arg Arg Xaa Ser Tyr
1 5

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2625 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 796..2580

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
CATTTTCTTA ATTCTTTTAT GTGCTTTTAC TACTTTGTTT AGTTCAAAAC AATAGTCGTT      60

ATTCTTAGGT ACTATAGCAT AAGACAAGAA AAGAAAAATA AGGGACAAAT AACATTAGCA     120

GAAGTACGGT ATATTTTACT GTTACTTATA TACTTTCAAG AAGATGAGTT AAATCGGTAG     180

CCAGTGTAGA AAAATAATAA TAAGGGTCAT CGATCCTTCG CATTTTATTA TCCAATTAAA     240

GATACGAATC ACGGCAAACT ATATTCAAAG CTCATAGATA ATCGTCGTAA GGCTGACACT     300

GCAGAAGAAA AGTCATAATT TGAATACTAG CCGGTATGAA ACTGTGATTG ATTAACCTGG     360

GGTTACCTAA AGAGAACATA AGTAATACTC ATGACAGAAT CAAAACACAA TACAAAATTT     420

ATCCGAACCT CGGCCCGACT GCGGCTCGCC GGGAAAGGGG ACAACCGCTT CTATCCGTCG     480

ACTAACTTCA TCGGCCCAAT GGAAGCTATG ATATGGGGAT TTCCATTGAG CCGATAGCAA     540

TGTAGGGTAA TACTGTTGCG TATATAGTGA TAGTTATTGA ATTTTATTAC CCTGCGGGAA     600

TATTGAGACA TCACTAAGCA CGAATTTTAC GTCTGAGGAA AGTTGAATGA TGGCCAAATA     660

ACCAGGAAAA ACAAATATTG AATCCTTGTG AAGGATTCCA CAGTTGTTTA ATCCTCCTTA     720

AGCTCACTTA GTATCAATTG TCTAAATAAT ATTGCTTTGA ATCTGAAAAA AATAAAAGTA     780

CCTTCGCATT AGACA ATG TCA CTG CCG CTA CGA CAC GCA TTG GAG AAC GTT      831
                Met Ser Leu Pro Leu Arg His Ala Leu Glu Asn Val
                  1               5                  10

ACT TCT GTT GAT AGA ATT TTA GAG GAC TTA TTA GTA CGT TTT ATT ATA      879
Thr Ser Val Asp Arg Ile Leu Glu Asp Leu Leu Val Arg Phe Ile Ile
        15                  20                  25

AAT TGT CCG AAT GAA GAT TTA TCG AGT GTC GAG AGA GAG TTA TTT CAT      927
Asn Cys Pro Asn Glu Asp Leu Ser Ser Val Glu Arg Glu Leu Phe His
     30                  35                  40

TTT GAA GAA GCC TCA TGG TTT TAC ACG GAT TTC ATC AAA TTG ATG AAT      975
Phe Glu Glu Ala Ser Trp Phe Tyr Thr Asp Phe Ile Lys Leu Met Asn
 45                  50                  55                  60

CCA ACT TTA CCC TCC CTA AAG ATT AAA TCA TTT GCT CAA TTG ATC ATA     1023
Pro Thr Leu Pro Ser Leu Lys Ile Lys Ser Phe Ala Gln Leu Ile Ile
                65                  70                  75

AAA CTA TGT CCT CTG GTT TGG AAA TGG GAC ATA AGA GTG GAT GAG GCA     1071
Lys Leu Cys Pro Leu Val Trp Lys Trp Asp Ile Arg Val Asp Glu Ala
            80                  85                  90
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CTC CAG CAA TTC TCC AAG TAT AAG AAA AGT ATA CCG GTG AGG GGC GCT      1119
Leu Gln Gln Phe Ser Lys Tyr Lys Lys Ser Ile Pro Val Arg Gly Ala
         95                  100                 105

GCC ATA TTT AAC GAG AAC CTG AGT AAA ATT TTA TTG GTA CAG GGT ACT      1167
Ala Ile Phe Asn Glu Asn Leu Ser Lys Ile Leu Leu Val Gln Gly Thr
    110                 115                 120

GAA TCG GAT TCT TTG TCA TTC CCA AGG GGG AAG ATA TCT AAA GAT GAA      1215
Glu Ser Asp Ser Leu Ser Phe Pro Arg Gly Lys Ile Ser Lys Asp Glu
125                 130                 135                 140

AAT GAC ATA GAT TGT TGC ATT AGA GAA GTG AAA GAA GAA ATT GGT TTC      1263
Asn Asp Ile Asp Cys Cys Ile Arg Glu Val Lys Glu Glu Ile Gly Phe
                145                 150                 155

GAT TTG ACG GAC TAT ATT GAC GAC AAC CAA TTC ATT GAA AGA AAT ATT      1311
Asp Leu Thr Asp Tyr Ile Asp Asp Asn Gln Phe Ile Glu Arg Asn Ile
            160                 165                 170

CAA GGT AAA AAT TAC AAA ATA TTT TTG ATA TCT GGT GTT TCA GAA GTC      1359
Gln Gly Lys Asn Tyr Lys Ile Phe Leu Ile Ser Gly Val Ser Glu Val
        175                 180                 185

TTC AAT TTT AAA CCT CAA GTT AGA AAT GAA ATT GAT AAG ATA GAA TGG      1407
Phe Asn Phe Lys Pro Gln Val Arg Asn Glu Ile Asp Lys Ile Glu Trp
    190                 195                 200

TTC GAT TTT AAG AAA ATT TCT AAA ACA ATG TAC AAA TCA AAT ATC AAG      1455
Phe Asp Phe Lys Lys Ile Ser Lys Thr Met Tyr Lys Ser Asn Ile Lys
205                 210                 215                 220

TAT TAT CTG ATT AAT TCC ATG ATG AGA CCC TTA TCA ATG TGG TTA AGG      1503
Tyr Tyr Leu Ile Asn Ser Met Met Arg Pro Leu Ser Met Trp Leu Arg
                225                 230                 235

CAT CAG AGG CAA ATA AAA AAT GAA GAT CAA TTG AAA TCC TAT GCG GAA      1551
His Gln Arg Gln Ile Lys Asn Glu Asp Gln Leu Lys Ser Tyr Ala Glu
            240                 245                 250

GAA CAA TTG AAA TTG TTG TTG GGT ATC ACT AAG GAG GAG CAG ATT GAT      1599
Glu Gln Leu Lys Leu Leu Leu Gly Ile Thr Lys Glu Glu Gln Ile Asp
        255                 260                 265

CCC GGT AGA GAG TTG CTG AAT ATG TTA CAT ACT GCA GTG CAA GCT AAC      1647
Pro Gly Arg Glu Leu Leu Asn Met Leu His Thr Ala Val Gln Ala Asn
    270                 275                 280

AGT AAT AAT AAT GCG GTC TCC AAC GGA CAG GTA CCC TCG AGC CAA GAG      1695
Ser Asn Asn Asn Ala Val Ser Asn Gly Gln Val Pro Ser Ser Gln Glu
285                 290                 295                 300

CTT CAG CAT TTG AAA GAG CAA TCA GGA GAA CAC AAC CAA CAG AAG GAT      1743
Leu Gln His Leu Lys Glu Gln Ser Gly Glu His Asn Gln Gln Lys Asp
                305                 310                 315

CAG CAG TCA TCG TTT TCT TCT CAA CAA CAA CCT TCA ATA TTT CCA TCT      1791
Gln Gln Ser Ser Phe Ser Ser Gln Gln Gln Pro Ser Ile Phe Pro Ser
            320                 325                 330

CTT TCT GAA CCG TTT GCT AAC AAT AAG AAT GTT ATA CCA CCT ACT ATG      1839
Leu Ser Glu Pro Phe Ala Asn Asn Lys Asn Val Ile Pro Pro Thr Met
        335                 340                 345

CCA ATG GCT AAC GTA TTC ATG TCA AAT CCT CAA TTG TTT GCG ACA ATG      1887
Pro Met Ala Asn Val Phe Met Ser Asn Pro Gln Leu Phe Ala Thr Met
    350                 355                 360
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AAT GGC CAG CCT TTT GCA CCT TTC CCA TTT ATG TTA CCA TTA ACT AAC      1935
Asn Gly Gln Pro Phe Ala Pro Phe Pro Phe Met Leu Pro Leu Thr Asn
365                 370                 375                 380

AAT AGT AAT AGC GCT AAC CCT ATT CCA ACT CCG GTC CCC CCT AAT TTT      1983
Asn Ser Asn Ser Ala Asn Pro Ile Pro Thr Pro Val Pro Pro Asn Phe
                385                 390                 395

AAT GCT CCT CCG AAT CCG ATG GCT TTT GGT GTT CCA AAC ATG CAT AAC      2031
Asn Ala Pro Pro Asn Pro Met Ala Phe Gly Val Pro Asn Met His Asn
            400                 405                 410

CTT TCT GGA CCA GCA GTA TCT CAA CCG TTT TCC TTG CCT CCT GCT CCT      2079
Leu Ser Gly Pro Ala Val Ser Gln Pro Phe Ser Leu Pro Pro Ala Pro
        415                 420                 425

TTA CCG AGG GAC TCT GGT TAC AGC AGC TCC TCC CCT GGG CAG TTG TTA      2127
Leu Pro Arg Asp Ser Gly Tyr Ser Ser Ser Ser Pro Gly Gln Leu Leu
    430                 435                 440

GAT ATA CTA AAT TCG AAA AAG CCT GAC AGC AAC GTG CAA TCA AGC AAA      2175
Asp Ile Leu Asn Ser Lys Lys Pro Asp Ser Asn Val Gln Ser Ser Lys
445                 450                 455                 460

AAG CCA AAG CTT AAA ATC TTA CAG AGA GGA ACG GAC TTG AAT TCA CTC      2223
Lys Pro Lys Leu Lys Ile Leu Gln Arg Gly Thr Asp Leu Asn Ser Leu
                465                 470                 475

AAG CAA AAC AAT AAT GAT GAA ACT GCT CAT TCA AAC TCT CAA GCT TTG      2271
Lys Gln Asn Asn Asn Asp Glu Thr Ala His Ser Asn Ser Gln Ala Leu
            480                 485                 490

CTA GAT TTG TTG AAA AAA CCA ACA TCA TCG CAG AAG ATA CAC GCT TCC      2319
Leu Asp Leu Leu Lys Lys Pro Thr Ser Ser Gln Lys Ile His Ala Ser
        495                 500                 505

AAA CCA GAT ACT TCC TTT TTA CCA AAT GAC TCC GTA TCT GGT ATA CAA      2367
Lys Pro Asp Thr Ser Phe Leu Pro Asn Asp Ser Val Ser Gly Ile Gln
    510                 515                 520

GAT GCA GAA TAT GAA GAT TTC GAG AGT AGT TCA GAT GAA GAG GTG GAG      2415
Asp Ala Glu Tyr Glu Asp Phe Glu Ser Ser Ser Asp Glu Glu Val Glu
525                 530                 535                 540

ACA GCT AGA GAT GAA AGA AAT TCA TTG AAT GTA GAT ATT GGG GTG AAC      2463
Thr Ala Arg Asp Glu Arg Asn Ser Leu Asn Val Asp Ile Gly Val Asn
                545                 550                 555

GTT ATG CCA AGC GAA AAA GAC AGC CGA AGA AGT CAA AAG GAA AAA CCA      2511
Val Met Pro Ser Glu Lys Asp Ser Arg Arg Ser Gln Lys Glu Lys Pro
            560                 565                 570

AGG AAC GAC GCA AGC AAA ACA AAC TTG AAC GCT TCT GCA GAA TCT AAT      2559
Arg Asn Asp Ala Ser Lys Thr Asn Leu Asn Ala Ser Ala Glu Ser Asn
        575                 580                 585

AGT GTA GAA TGG GGG GCT GGG TAAATCTTCA CCCTCCGACT TCAGAGTAAC        2610
Ser Val Glu Trp Gly Ala Gly
    590                 595

ACAGAATCCA CAGTA                                                    2625
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(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 595 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

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Met Ser Leu Pro Leu Arg His Ala Leu Glu Asn Val Thr Ser Val Asp
 1               5                  10                  15

Arg Ile Leu Glu Asp Leu Leu Val Arg Phe Ile Ile Asn Cys Pro Asn
            20                  25                  30

Glu Asp Leu Ser Ser Val Glu Arg Glu Leu Phe His Phe Glu Glu Ala
        35                  40                  45

Ser Trp Phe Tyr Thr Asp Phe Ile Lys Leu Met Asn Pro Thr Leu Pro
    50                  55                  60

Ser Leu Lys Ile Lys Ser Phe Ala Gln Leu Ile Ile Lys Leu Cys Pro
65                  70                  75                  80

Leu Val Trp Lys Trp Asp Ile Arg Val Asp Glu Ala Leu Gln Gln Phe
                85                  90                  95

Ser Lys Tyr Lys Lys Ser Ile Pro Val Arg Gly Ala Ala Ile Phe Asn
            100                 105                 110

Glu Asn Leu Ser Lys Ile Leu Leu Val Gln Gly Thr Glu Ser Asp Ser
        115                 120                 125

Leu Ser Phe Pro Arg Gly Lys Ile Ser Lys Asp Glu Asn Asp Ile Asp
    130                 135                 140

Cys Cys Ile Arg Glu Val Lys Glu Glu Ile Gly Phe Asp Leu Thr Asp
145                 150                 155                 160

Tyr Ile Asp Asp Asn Gln Phe Ile Glu Arg Asn Ile Gln Gly Lys Asn
                165                 170                 175

Tyr Lys Ile Phe Leu Ile Ser Gly Val Ser Glu Val Phe Asn Phe Lys
            180                 185                 190

Pro Gln Val Arg Asn Glu Ile Asp Lys Ile Glu Trp Phe Asp Phe Lys
        195                 200                 205

Lys Ile Ser Lys Thr Met Tyr Lys Ser Asn Ile Lys Tyr Tyr Leu Ile
    210                 215                 220

Asn Ser Met Met Arg Pro Leu Ser Met Trp Leu Arg His Gln Arg Gln
225                 230                 235                 240

Ile Lys Asn Glu Asp Gln Leu Lys Ser Tyr Ala Glu Glu Gln Leu Lys
                245                 250                 255

Leu Leu Leu Gly Ile Thr Lys Glu Glu Gln Ile Asp Pro Gly Arg Glu
            260                 265                 270

Leu Leu Asn Met Leu His Thr Ala Val Gln Ala Asn Ser Asn Asn Asn
        275                 280                 285

Ala Val Ser Asn Gly Gln Val Pro Ser Ser Gln Glu Leu Gln His Leu
    290                 295                 300
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Lys Glu Gln Ser Gly Glu His Asn Gln Gln Lys Asp Gln Gln Ser Ser
305                 310                 315                 320

Phe Ser Ser Gln Gln Gln Pro Ser Ile Phe Pro Ser Leu Ser Glu Pro
                325                 330                 335

Phe Ala Asn Asn Lys Asn Val Ile Pro Pro Thr Met Pro Met Ala Asn
            340                 345                 350

Val Phe Met Ser Asn Pro Gln Leu Phe Ala Thr Met Asn Gly Gln Pro
        355                 360                 365

Phe Ala Pro Phe Pro Phe Met Leu Pro Leu Thr Asn Asn Ser Asn Ser
    370                 375                 380

Ala Asn Pro Ile Pro Thr Pro Val Pro Pro Asn Phe Asn Ala Pro Pro
385                 390                 395                 400

Asn Pro Met Ala Phe Gly Val Pro Asn Met His Asn Leu Ser Gly Pro
                405                 410                 415

Ala Val Ser Gln Pro Phe Ser Leu Pro Pro Ala Pro Leu Pro Arg Asp
            420                 425                 430

Ser Gly Tyr Ser Ser Ser Ser Pro Gly Gln Leu Leu Asp Ile Leu Asn
        435                 440                 445

Ser Lys Lys Pro Asp Ser Asn Val Gln Ser Ser Lys Lys Pro Lys Leu
    450                 455                 460

Lys Ile Leu Gln Arg Gly Thr Asp Leu Asn Ser Leu Lys Gln Asn Asn
465                 470                 475                 480

Asn Asp Glu Thr Ala His Ser Asn Ser Gln Ala Leu Leu Asp Leu Leu
                485                 490                 495

Lys Lys Pro Thr Ser Ser Gln Lys Ile His Ala Ser Lys Pro Asp Thr
            500                 505                 510

Ser Phe Leu Pro Asn Asp Ser Val Ser Gly Ile Gln Asp Ala Glu Tyr
        515                 520                 525

Glu Asp Phe Glu Ser Ser Ser Asp Glu Glu Val Glu Thr Ala Arg Asp
    530                 535                 540

Glu Arg Asn Ser Leu Asn Val Asp Ile Gly Val Asn Val Met Pro Ser
545                 550                 555                 560

Glu Lys Asp Ser Arg Arg Ser Gln Lys Glu Lys Pro Arg Asn Asp Ala
                565                 570                 575

Ser Lys Thr Asn Leu Asn Ala Ser Ala Glu Ser Asn Ser Val Glu Trp
            580                 585                 590

Gly Ala Gly
        595
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(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6854 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 2050..4053

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

AGCTTCTCCC TTTTCCTTCA GTGCTGCTAC TCTCTGCTCT CCACTTAAGT GTTACAATTA 60
ATTTGCAGCT AGTTTGCAGT TCGTACAACC TCGCCTATTC TTGTAACGAA GAAGAACGTA 120
TTTATAATAT TGGGCTGTAA TGTGTTGAGT TTAGTAATAG ATAAAGTAGG ACAGAGTTCT 180
GTCTTTGTTT ATCTATGGGG TTCAGAGTGA TAAGGGGCAG GATAAGGAAG TTAAAAAAAA 240
AAAGGTTACG TTATATAACG AAAGAAAAGA AACGAGCGAA GTGCCAACTA TAGCCCAATA 300
TCAAGAATGC AAGTCAGCAA AGTACAGTAA TCGTATGAAG ATACGCGATG CGTAATATCC 360
CTCAAGGGCT CCGGATCAGA AAAGCTAAGG GAAGATCCTT ACATTACACG GCGTGCGACA 420
GACTCGAACC ACAGCTAACT TCTCGTGAAA AGATGGCTTC AACTTCGCTC TTGCAATAAC 480
TTTGAAACAC ACGAACAAAG GTTTATTGCG CTTGATTAAC GTTGGAAGTA TATGATACTA 540
ATACTACTTT GTTCTCTAAG TCATCGCTAT ATGTTTATCT CGAGGAAAAG GTGCACGGCG 600
GTACACAATT ACTTCGCCGT TTCGGGTAAA ACAAGTGTTA CATTTATAAT ATATATGTAT 660
ATATGTATGT GCGCGTAAGT ATATGCCGTT CATAACAAAT CATCTTCTTG TTGCTGGATG 720
GACTCCTTAA TTTTATTCAA AATGGTAATT TTCCATTTAT CTAGTCTCAT AAAATTGTCA 780
AACTCCTTAC AGTGTTCGCT TAGCTGCTCG CTATCACCTT CATTAACAGC ATCGATTAAA 840
CTTTTCAAGA AATTTGACTC CCTTGAATCC GCAAAATTCG GATCTTCACT TTGACCCTCT 900
TGTAAAGTTC TTGCAGCAGC GACTGCATCA GTAGCAGCTA GCTGACAAAG CCCTTTTTTT 960
AGGAAGTAAT CCTTCAAACT CCATTGGCTC AATCTATTGC CCATGCTGCT CTTGATCAAC 1020
TTCGAATATA TATCACTTGC TTCAATATAT TGACCGTCAA GAGCCTTTAG ATCTGCGCAT 1080
TTGATAAAAC ACTTATTCGA TAATGCTACC GACTGGTCTT GGGCATACCA CTCACCAGCG 1140
AGCTCATAGC AATCTATAGC TTTTGCATAG TCATGCAAAT CATTTTCTAG AATTTCTCCA 1200
AGCTCAAACT TGAAATTAGC ACCTCTCCGG AACTGCCCCC TATGAGTAAA AATTTGAATA 1260
GCATTTTCTA ATGAATCCAC GGCGTTCACA GAGTTTCCAC CGCTTTTAAA GCATTTATAA 1320
GCCTCTACGT AGGTATTTCC TGCTTCGTCT TCATTACCAG CCTTTTTCTG ATAGTCAGCA 1380
GCTTTCAAAA ACGAGTCTCC TGCCAAGTTT AACTCTTTTC TTAGACGGTA AATGGTGGCT 1440
GCTTGGACAC AAAGATCAGC AGCCTCCTCA AACTTGTATG AATCAGAACC GCTAAACAAT 1500
TTCATGAAAC CCGATGAAGG AACACCCTTC TTCTCAGCCT TAACACAACG GGAAATATCA 1560
ATTCCCGTAT TTCAATGTTA GTAATTTGCC TTCGTAAATT ACGGAATCAC ATAGCTTTCA 1620
TTTTGTTCCT TTGATATATT TCCCTACTAC ATACTCTTTT CAATAACTCT ACAGGGTCTG 1680
ACATTTTTAA CTTTCAGGTT AATGATGGTG TTCTTACTAT ATTCTCGAGT CGTACAGAAG 1740
TTAGTTCAGA TAAACTGCTT CGGTGCTGCC CACTTCTTAT CATTACTTCA ACTTTACCTT 1800

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CCCTATACCT GTGTGTCCTT ATTAATTCAA GTTAATCCGA GGTAATAGAT TAGGGTAACC    1860

TTCAATGATG TCACGAAACA CGGATGCTGC AACTTTGCGA TTTTTTCCTG GAAAAGAATA    1920

ACAATTAAAG GCAGCCTTTC AGCTGAGATT ACCAGCAGGT CTTTGGAGAT TAGCGCAAGA    1980

AGAAGTGTGA TATAGTACTC ATAGAGGCAG GCTACAGACT AGGGAAAGCG TGTTCAACAA    2040

CAATAAGAA ATG GAG ACC AGT TCT TTT GAG AAT GCT CCT CCT GCA GCC          2088
          Met Glu Thr Ser Ser Phe Glu Asn Ala Pro Pro Ala Ala
            1               5                  10

ATC AAT GAT GCT CAG GAT AAT AAT ATA AAT ACG GAG ACT AAT GAC CAG      2136
Ile Asn Asp Ala Gln Asp Asn Asn Ile Asn Thr Glu Thr Asn Asp Gln
     15                  20                  25

GAA ACA AAT CAG CAA TCT ATC GAA ACT AGA GAT GCA ATT GAC AAA GAA      2184
Glu Thr Asn Gln Gln Ser Ile Glu Thr Arg Asp Ala Ile Asp Lys Glu
 30                  35                  40                  45

AAC GGT GTG CAA ACG GAA ACT GGT GAG AAC TCT GCA AAA AAT GCC GAA      2232
Asn Gly Val Gln Thr Glu Thr Gly Glu Asn Ser Ala Lys Asn Ala Glu
                 50                  55                  60

CAA AAC GTT TCT TCT ACA AAT TTG AAT AAT GCC CCC ACC AAT GGT GCT      2280
Gln Asn Val Ser Ser Thr Asn Leu Asn Asn Ala Pro Thr Asn Gly Ala
           65                  70                  75

TTG GAC GAT GAT GTT ATC CCA AAT GCT ATT GTT ATT AAA AAC ATT CCG      2328
Leu Asp Asp Asp Val Ile Pro Asn Ala Ile Val Ile Lys Asn Ile Pro
      80                  85                  90

TTT GCT ATT AAA AAA GAG CAA TTG TTA GAC ATT ATT GAA GAA ATG GAT      2376
Phe Ala Ile Lys Lys Glu Gln Leu Leu Asp Ile Ile Glu Glu Met Asp
 95                  100                 105

CTT CCC CTT CCT TAT GCC TTC AAT TAC CAC TTT GAT AAC GGT ATT TTC      2424
Leu Pro Leu Pro Tyr Ala Phe Asn Tyr His Phe Asp Asn Gly Ile Phe
110                 115                 120                 125

AGA GGA CTA GCC TTT GCG AAT TTC ACC ACT CCT GAA GAA ACT ACT CAA      2472
Arg Gly Leu Ala Phe Ala Asn Phe Thr Thr Pro Glu Glu Thr Thr Gln
                130                 135                 140

GTG ATA ACT TCT TTG AAT GGA AAG GAA ATC AGC GGG AGG AAA TTG AAA      2520
Val Ile Thr Ser Leu Asn Gly Lys Glu Ile Ser Gly Arg Lys Leu Lys
           145                 150                 155

GTG GAA TAT AAA AAA ATG CTT CCC CAA GCT GAA AGA GAA AGA ATC GAG      2568
Val Glu Tyr Lys Lys Met Leu Pro Gln Ala Glu Arg Glu Arg Ile Glu
      160                 165                 170

AGG GAG AAG AGA GAG AAA AGA GGA CAA TTA GAA GAA CAA CAC AGA TCG      2616
Arg Glu Lys Arg Glu Lys Arg Gly Gln Leu Glu Glu Gln His Arg Ser
 175                 180                 185

TCA TCT AAT CTT TCT TTG GAT TCT TTA TCT AAA ATG AGT GGA AGC GGA      2664
Ser Ser Asn Leu Ser Leu Asp Ser Leu Ser Lys Met Ser Gly Ser Gly
190                 195                 200                 205

AAC AAT AAT ACT TCT AAC AAT CAA TTA TTC TCG ACT CTA ATG AAC GGC      2712
Asn Asn Asn Thr Ser Asn Asn Gln Leu Phe Ser Thr Leu Met Asn Gly
                210                 215                 220

ATT AAT GCT AAT AGC ATG ATG AAC AGT CCA ATG AAT AAT ACC ATT AAC      2760
Ile Asn Ala Asn Ser Met Met Asn Ser Pro Met Asn Asn Thr Ile Asn
           225                 230                 235
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AAT AAC AGT TCT AAT AAC AAC AAT AGT GGT AAC ATC ATT CTG AAC CAA      2808
Asn Asn Ser Ser Asn Asn Asn Asn Ser Gly Asn Ile Ile Leu Asn Gln
        240                 245                 250

CCT TCA CTT TCT GCC CAA CAT ACT TCT TCA TCG TTG TAC CAA ACA AAC      2856
Pro Ser Leu Ser Ala Gln His Thr Ser Ser Ser Leu Tyr Gln Thr Asn
    255                 260                 265

GTT AAT AAT CAA GCC CAG ATG TCC ACT GAG AGA TTT TAT GCG CCT TTA      2904
Val Asn Asn Gln Ala Gln Met Ser Thr Glu Arg Phe Tyr Ala Pro Leu
270                 275                 280                 285

CCA TCA ACT TCC ACT TTG CCT CTC CCA CCC CAA CAA CTG GAC TTC AAT      2952
Pro Ser Thr Ser Thr Leu Pro Leu Pro Pro Gln Gln Leu Asp Phe Asn
                290                 295                 300

GAC CCT GAC ACT TTG GAA ATT TAT TCC CAA TTA TTG TTA TTT AAG GAT      3000
Asp Pro Asp Thr Leu Glu Ile Tyr Ser Gln Leu Leu Leu Phe Lys Asp
            305                 310                 315

AGA GAA AAG TAT TAT TAC GAG TTG GCT TAT CCC ATG GGT ATA TCC GCT      3048
Arg Glu Lys Tyr Tyr Tyr Glu Leu Ala Tyr Pro Met Gly Ile Ser Ala
        320                 325                 330

TCC CAC AAG AGA ATT ATC AAT GTT TTG TGC TCG TAC TTA GGG CTA GTA      3096
Ser His Lys Arg Ile Ile Asn Val Leu Cys Ser Tyr Leu Gly Leu Val
    335                 340                 345

GAA GTA TAT GAT CCA AGA TTT ATT ATT ATC AGA AGA AAG ATT CTG GAT      3144
Glu Val Tyr Asp Pro Arg Phe Ile Ile Ile Arg Arg Lys Ile Leu Asp
350                 355                 360                 365

CAT GCT AAT TTA CAA TCT CAT TTG CAA CAA CAA GGT CAA ATG ACA TCT      3192
His Ala Asn Leu Gln Ser His Leu Gln Gln Gln Gly Gln Met Thr Ser
                370                 375                 380

GCT CAT CCT TTG CAG CCA AAC TCC ACT GGC GGC TCC ATG AAT AGG TCA      3240
Ala His Pro Leu Gln Pro Asn Ser Thr Gly Gly Ser Met Asn Arg Ser
            385                 390                 395

CAA TCT TAT ACA AGT TTG TTA CAG GCC CAT GCA GCA GCT GCA GCG AAT      3288
Gln Ser Tyr Thr Ser Leu Leu Gln Ala His Ala Ala Ala Ala Ala Asn
        400                 405                 410

AGT ATT AGC AAT CAG GCC GTT AAC AAT TCT TCC AAC AGC AAT ACT ATT      3336
Ser Ile Ser Asn Gln Ala Val Asn Asn Ser Ser Asn Ser Asn Thr Ile
    415                 420                 425

AAC AGT AAT AAC GGT AAC GGT AAC AAT GTC ATC ATT AAT AAC AAT AGC      3384
Asn Ser Asn Asn Gly Asn Gly Asn Asn Val Ile Ile Asn Asn Asn Ser
430                 435                 440                 445

GCC AGC TCA ACA CCA AAA ATT TCT TCA CAG GGA CAA TTC TCC ATG CAA      3432
Ala Ser Ser Thr Pro Lys Ile Ser Ser Gln Gly Gln Phe Ser Met Gln
                450                 455                 460

CCA ACA CTA ACC TCA CCT AAA ATG AAC ATA CAC CAT AGT TCT CAA TAC      3480
Pro Thr Leu Thr Ser Pro Lys Met Asn Ile His His Ser Ser Gln Tyr
            465                 470                 475

AAT TCC GCA GAC CAA CCG CAA CAA CCT CAA CCA CAA ACA CAG CAA AAT      3528
Asn Ser Ala Asp Gln Pro Gln Gln Pro Gln Pro Gln Thr Gln Gln Asn
        480                 485                 490

GTT CAG TCA GCT GCG CAA CAA CAA CAA TCT TTT TTA AGA CAA CAA GCT      3576
Val Gln Ser Ala Ala Gln Gln Gln Gln Ser Phe Leu Arg Gln Gln Ala
    495                 500                 505
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ACT TTA ACA CCA TCC TCA AGA ATT CCA TCC GGT TAT TCT GCC AAC CAT      3624
Thr Leu Thr Pro Ser Ser Arg Ile Pro Ser Gly Tyr Ser Ala Asn His
510                 515                 520                 525

TAT CAA ATC AAT TCC GTT AAT CCC TTA CTG AGA AAT TCT CAA ATT TCA      3672
Tyr Gln Ile Asn Ser Val Asn Pro Leu Leu Arg Asn Ser Gln Ile Ser
            530                 535                 540

CCT CCA AAT TCA CAA ATC CCA ATC AAC AGC CAA ACC CTA TCC CAA GCG      3720
Pro Pro Asn Ser Gln Ile Pro Ile Asn Ser Gln Thr Leu Ser Gln Ala
        545                 550                 555

CAA CCA CCA GCA CAG TCC CAA ACT CAA CAA CGG GTA CCA GTG GCA TAC      3768
Gln Pro Pro Ala Gln Ser Gln Thr Gln Gln Arg Val Pro Val Ala Tyr
    560                 565                 570

CAA AAT GCT TCA TTG TCT TCC CAG CAG TTG TAC AAC CTT AAC GGC CCA      3816
Gln Asn Ala Ser Leu Ser Ser Gln Gln Leu Tyr Asn Leu Asn Gly Pro
575                 580                 585

TCT TCA GCA AAC TCA CAG TCC CAA CTG CTT CCA CAG CAC ACA AAT GGC      3864
Ser Ser Ala Asn Ser Gln Ser Gln Leu Leu Pro Gln His Thr Asn Gly
590                 595                 600                 605

TCA GTA CAT TCT AAT TTC TCA TAT CAG TCT TAT CAC GAT GAG TCC ATG      3912
Ser Val His Ser Asn Phe Ser Tyr Gln Ser Tyr His Asp Glu Ser Met
            610                 615                 620

TTG TCC GCA CAC AAT TTG AAT AGT GCC GAC TTG ATC TAT AAA TCT TTG      3960
Leu Ser Ala His Asn Leu Asn Ser Ala Asp Leu Ile Tyr Lys Ser Leu
        625                 630                 635

AGT CAC TCT GGA CTA GAT GAT GGC TTG GAA CAG GGC TTG AAT CGT TCT      4008
Ser His Ser Gly Leu Asp Asp Gly Leu Glu Gln Gly Leu Asn Arg Ser
    640                 645                 650

TTA AGC GGA CTG GAT TTA CAA AAC CAA AAC AAG AAG AAT CTA TGG          4053
Leu Ser Gly Leu Asp Leu Gln Asn Gln Asn Lys Lys Asn Leu Trp
655                 660                 665

TAATATATAC TTCCATTATT CTATGATTAT AGAGTTTGTT TGGTATTTGT ATATCGCACG    4113

ATACAAGTAA TGAGGGGTGC TTACACAAGA TAAAAGATAA AAAAATATAT ATATATAATA    4173

AAAACCATCA AAAACACCAT TGAAAAAAAA TATAAAAAAA AAAAAAAATA ACCGAATATG    4233

AATATGAAAT TAATGATCAT GATGAAGTTA ATTTTTACTG AGAAACGTCA CCTAATGTCG    4293

ATGAAACGAT GATAATGAAT GAATGATGAG GCTACTTTAA GTAACGCAAT GTAATCAAGC    4353

CAAAATTATC CCTCTTTTTT TTTTTTCCCT CTTTTGAGAT TTTATTTTTA ACCTACTACT    4413

TACTTTTTTT TTTTGAACGT TCTTTTCCCA CATACTTTTA TATATGGTAT TTATATGTAC    4473

GATGTTTAAT CACAGAGATG TTTCTACCTT ACTCGATATT GTTTTTGCAT TAATTGATAT    4533

CTTGCTCACT GCATCATTGG CGGTATTTGT AGTATATAGA AAGTCGGGTA ACAATAATTT    4593

ATTGACATTT CTTTGTTTAC AATGATCAGA GAAGAGCAGA AAGTTTCATA GTCAAACGTT    4653

CAGGCCAATT GAACAAGAAA TTATTCGTTT TTTTAGTCGT TGAGTGTTCA ACTGACATGC    4713

TATTTTGGTG GTTCTTGATT AATTGGGGGC TTCATTGTTT GAAATAAAGA GTCGGGAAAA    4773

TAGCACAGAA ACAAAGCATA TTAAAAGAGG CAAAAGAAGA AAGAACGAAT ATAAAAGGTA    4833

AAAAAGGAAA AGCATTGCTA TTCTTTTCTC ATAGGTGTTA TTCATACCGC CCTCTCTCTT    4893
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CTTCCTTCTT CATTAATTAG TCTCCGTATA ATTTGCAGAT AATGTCATTA ACAGCAAACG 4953

ACGAATCGCC AAAACCCAAA AAAAATGCAT TATTGAAAAA CTTAGAGATC GATGATCTGA 5013

TACATTCTCA ATTTGTCAGA AGCGATACAA ATGGACATAG AACTACAAGA CGACTATTCA 5073

ACTCCGATGC CAGTATATCA CATCGAATAA GAGGAAGTGT TCGGTCTGAT AAAGGCCTTA 5133

ATAAAATAAA AAAAGGGTTG ATTTCCCAGC AGTCCAAACT TGCGTCAGAA AATTCTTCTC 5193

AAAATATCGT TAATAGGGAC AATAAGATGG GAGCAGTAAG TTTCCCCATT ATTGAACCTA 5253

ATATTGAAGT CAGCGAGGAG TTGAAGGTTA GAATTAAGTA TGATTCTATC AAATTTTTCA 5313

ATTTTGAAAG ACTAATATCT AAATCTTCAG TCATAGCACC TTTAGTTAAC AAAAATATAA 5373

CATCATCCGG TCCTCTAATC GGGTTTCAAA GAAGAGTTAA CAGGTTAAAG CAAACATGGG 5433

ATCTAGCAAC CGAAAACATG GAGTACCCAT ATTCTTCTGA TAATACGCCA TTCAGGGATA 5493

ACGATTCTTG GCAATGGTAC GTACCATACG GCGGAACAAT AAAAAAAATG AAAGATTTCA 5553

GTACAAAAAG AACTTTACCC ACCTGGGAAG ATAAAATAAA GTTTCTTACA TTTTTAGAAA 5613

ACTCTAAGTC TGCAACGTAC ATTAATGGTA ACGTATCACT TTGCAATCAT AATGAAACCG 5673

ATCAAGAAAA CGAAGATAGG AAAAAAAGGA AAGGGAAAGT ACCAAGAATC AAAAATAAAG 5733

TGTGGTTTTC CCAGATAGAA TACATTGTTC TTCGAAATTA TGAAATTAAA CCTTGGTATA 5793

CATCTCCTTT TCCGGAACAC ATCAACCAAA ATAAAATGGT TTTTATATGT GAGTTCTGCC 5853

TAAAATATAT GACTTCTCGA TATACTTTTT ATAGACACCA ACTAAAGTGT CTAACTTTTA 5913

AGCCCCCCGG AAATGAAATT TATCGCGACG GTAAGCTGTC TGTTTGGGAA ATTGATGGGC 5973

GGGAGAATGT CTTGTATTGT CAAAATCTTT GCCTGTTGGC AAAATGTTTT ATCAATTCTA 6033

AGACTTTGTA TTACGATGTT GAACCGTTTA TATTCTATAT TCTAACGGAG AGAGAGGATA 6093

CAGAGAACCA TCCCTATCAA AACGCAGCCA AATTCCATTT CGTAGGCTAT TTCTCCAAGG 6153

AAAAATTCAA CTCCAATGAC TATAACCTAA GTTGTATTTT AACTCTACCC ATATACCAGA 6213

GGAAAGGATA TGGTCAGTTT TTGATGGAAT TTTCATATTT ATTATCCAGA AAGGAGTCAA 6273

AATTTGGAAC TCCTGAAAAA CCATTGTCGG ATTTAGGATT ATTGACTTAC AGAACGTTTT 6333

GGAAGATAAA ATGTGCTGAA GTGCTATTAA AATTAAGAGA CAGTGCTAGA CGTCGATCAA 6393

ATAATAAAAA TGAAGATACT TTTCAGCAGG TTAGCCTAAA CGATATCGCT AAACTAACAG 6453

GAATGATACC AACAGACGTT GTGTTTGGAT TGGAACAACT TCAAGTTTTG TATCGCCATA 6513

AAACACGCTC ATTATCCAGT TTGGATGATT TCAACTATAT TATTAAAATC GATTCTTGGA 6573

ACAGGATTGA AAATATTTAC AAAACTTGGA GCTCAAAAAA CTATCCTCGC GTCAAATATG 6633

ACAAACTATT GTGGGAACCT ATTATATTAG GGCCGTCATT TGGTATAAAT GGGATGATGA 6693

ACTTAGAACC CACCGCATTA GCGGACGAAG CTCTTACAAA TGAAACTATG GCTCCGGTAA 6753

TTTCGAATAA CACACATATA GAAAACTATA ACAACAGTAG AGCACATAAT AAACGCAGAA 6813

GAAGAAGAAG AAGAAGTAGT GAGCACAAAA CATCCAAGCT T 6854

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 668 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

```
Met Glu Thr Ser Ser Phe Glu Asn Ala Pro Pro Ala Ala Ile Asn Asp
 1               5                  10                  15

Ala Gln Asp Asn Asn Ile Asn Thr Glu Thr Asn Asp Gln Glu Thr Asn
            20                  25                  30

Gln Gln Ser Ile Glu Thr Arg Asp Ala Ile Asp Lys Glu Asn Gly Val
        35                  40                  45

Gln Thr Glu Thr Gly Glu Asn Ser Ala Lys Asn Ala Glu Gln Asn Val
    50                  55                  60

Ser Ser Thr Asn Leu Asn Asn Ala Pro Thr Asn Gly Ala Leu Asp Asp
65                  70                  75                  80

Asp Val Ile Pro Asn Ala Ile Val Ile Lys Asn Ile Pro Phe Ala Ile
                85                  90                  95

Lys Lys Glu Gln Leu Leu Asp Ile Ile Glu Glu Met Asp Leu Pro Leu
            100                 105                 110

Pro Tyr Ala Phe Asn Tyr His Phe Asp Asn Gly Ile Phe Arg Gly Leu
        115                 120                 125

Ala Phe Ala Asn Phe Thr Thr Pro Glu Glu Thr Thr Gln Val Ile Thr
    130                 135                 140

Ser Leu Asn Gly Lys Glu Ile Ser Gly Arg Lys Leu Lys Val Glu Tyr
145                 150                 155                 160

Lys Lys Met Leu Pro Gln Ala Glu Arg Glu Arg Ile Glu Arg Glu Lys
                165                 170                 175

Arg Glu Lys Arg Gly Gln Leu Glu Glu Gln His Arg Ser Ser Ser Asn
            180                 185                 190

Leu Ser Leu Asp Ser Leu Ser Lys Met Ser Gly Ser Gly Asn Asn Asn
        195                 200                 205

Thr Ser Asn Asn Gln Leu Phe Ser Thr Leu Met Asn Gly Ile Asn Ala
    210                 215                 220

Asn Ser Met Met Asn Ser Pro Met Asn Asn Thr Ile Asn Asn Asn Ser
225                 230                 235                 240

Ser Asn Asn Asn Asn Ser Gly Asn Ile Ile Leu Asn Gln Pro Ser Leu
                245                 250                 255

Ser Ala Gln His Thr Ser Ser Ser Leu Tyr Gln Thr Asn Val Asn Asn
            260                 265                 270

Gln Ala Gln Met Ser Thr Glu Arg Phe Tyr Ala Pro Leu Pro Ser Thr
        275                 280                 285

Ser Thr Leu Pro Leu Pro Pro Gln Gln Leu Asp Phe Asn Asp Pro Asp
    290                 295                 300
```

Thr Leu Glu Ile Tyr Ser Gln Leu Leu Leu Phe Lys Asp Arg Glu Lys
305 310 315 320

Tyr Tyr Tyr Glu Leu Ala Tyr Pro Met Gly Ile Ser Ala Ser His Lys
325 330 335

Arg Ile Ile Asn Val Leu Cys Ser Tyr Leu Gly Leu Val Glu Val Tyr
340 345 350

Asp Pro Arg Phe Ile Ile Ile Arg Arg Lys Ile Leu Asp His Ala Asn
355 360 365

Leu Gln Ser His Leu Gln Gln Gln Gly Gln Met Thr Ser Ala His Pro
370 375 380

Leu Gln Pro Asn Ser Thr Gly Gly Ser Met Asn Arg Ser Gln Ser Tyr
385 390 395 400

Thr Ser Leu Leu Gln Ala His Ala Ala Ala Ala Ala Asn Ser Ile Ser
405 410 415

Asn Gln Ala Val Asn Asn Ser Ser Asn Ser Asn Thr Ile Asn Ser Asn
420 425 430

Asn Gly Asn Gly Asn Asn Val Ile Ile Asn Asn Asn Ser Ala Ser Ser
435 440 445

Thr Pro Lys Ile Ser Ser Gln Gly Gln Phe Ser Met Gln Pro Thr Leu
450 455 460

Thr Ser Pro Lys Met Asn Ile His His Ser Ser Gln Tyr Asn Ser Ala
465 470 475 480

Asp Gln Pro Gln Gln Pro Gln Pro Gln Thr Gln Gln Asn Val Gln Ser
485 490 495

Ala Ala Gln Gln Gln Gln Ser Phe Leu Arg Gln Gln Ala Thr Leu Thr
500 505 510

Pro Ser Ser Arg Ile Pro Ser Gly Tyr Ser Ala Asn His Tyr Gln Ile
515 520 525

Asn Ser Val Asn Pro Leu Leu Arg Asn Ser Gln Ile Ser Pro Pro Asn
530 535 540

Ser Gln Ile Pro Ile Asn Ser Gln Thr Leu Ser Gln Ala Gln Pro Pro
545 550 555 560

Ala Gln Ser Gln Thr Gln Gln Arg Val Pro Val Ala Tyr Gln Asn Ala
565 570 575

Ser Leu Ser Ser Gln Gln Leu Tyr Asn Leu Asn Gly Pro Ser Ser Ala
580 585 590

Asn Ser Gln Ser Gln Leu Leu Pro Gln His Thr Asn Gly Ser Val His
595 600 605

Ser Asn Phe Ser Tyr Gln Ser Tyr His Asp Glu Ser Met Leu Ser Ala
610 615 620

His Asn Leu Asn Ser Ala Asp Leu Ile Tyr Lys Ser Leu Ser His Ser
625 630 635 640

Gly Leu Asp Asp Gly Leu Glu Gln Gly Leu Asn Arg Ser Leu Ser Gly
645 650 655

Leu Asp Leu Gln Asn Gln Asn Lys Lys Asn Leu Trp
660 665

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2814 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..696

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

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GAA TTC CAA TAC ACC AAA CAG CTG CAT TTC CCT GTG GGG CCC AAA TCC          48
Glu Phe Gln Tyr Thr Lys Gln Leu His Phe Pro Val Gly Pro Lys Ser
  1               5                  10                  15

ACA AAC TGT GAG GTA GCG GAA ATT CTT TTA CAC TGC GAC TGG GAA AGG          96
Thr Asn Cys Glu Val Ala Glu Ile Leu Leu His Cys Asp Trp Glu Arg
            20                  25                  30

TAC ATA AAT GTT TTA AGT ATA ACA AGA ACA CCA AAT GTT CCT AGT GGT         144
Tyr Ile Asn Val Leu Ser Ile Thr Arg Thr Pro Asn Val Pro Ser Gly
        35                  40                  45

ACC AGT TTC AGC ACC AGA ACG AGG TAC ATG TTC CGA TGG GAT GAC CAG         192
Thr Ser Phe Ser Thr Arg Thr Arg Tyr Met Phe Arg Trp Asp Asp Gln
    50                  55                  60

GGG CAA GGT TGC ATA TTA AAA ATA AGT TTT TGG GTG GAC TGG AAC GCA         240
Gly Gln Gly Cys Ile Leu Lys Ile Ser Phe Trp Val Asp Trp Asn Ala
65                  70                  75                  80

TCC AGT TGG ATC AAG CCA ATG GTA GAG AGC AAT TGT AAA AAT GGA CAA         288
Ser Ser Trp Ile Lys Pro Met Val Glu Ser Asn Cys Lys Asn Gly Gln
                85                  90                  95

ATT AGC GCC ACT AAG GAC TTG GTA AAG TTA GTC GAA GAA TTT GTA GAG         336
Ile Ser Ala Thr Lys Asp Leu Val Lys Leu Val Glu Glu Phe Val Glu
            100                 105                 110

AAA TAC GTG GAA TTG AGC AAA GAA AAA GCA GAT ACA CTC AAG CCG TTG         384
Lys Tyr Val Glu Leu Ser Lys Glu Lys Ala Asp Thr Leu Lys Pro Leu
        115                 120                 125

CCC AGT GTT ACA TCT TTT GGA TCA CCT AGG AAA GTG GCA GCA CCG GAG         432
Pro Ser Val Thr Ser Phe Gly Ser Pro Arg Lys Val Ala Ala Pro Glu
    130                 135                 140

CTG TCG ATG GTA CAG CCG GAG TCG AAA CCA GAA GCT GAG GCG GAA ATC         480
Leu Ser Met Val Gln Pro Glu Ser Lys Pro Glu Ala Glu Ala Glu Ile
145                 150                 155                 160

TCA GAA ATA GGC AGC GAC AGA TGG AGG TTT AAC TGG GTG AAC ATA ATA         528
Ser Glu Ile Gly Ser Asp Arg Trp Arg Phe Asn Trp Val Asn Ile Ile
                165                 170                 175
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ATC TTG GTG CTC TTG GTG TTA AAT CTG CTG TAT TTA ATG AAG TTG AAC        576
Ile Leu Val Leu Leu Val Leu Asn Leu Leu Tyr Leu Met Lys Leu Asn
            180                 185                 190

AAG AAG ATG GAT AAG CTG ACG AAC CTC ATG ACC CAC AAG GAC GAA GTT        624
Lys Lys Met Asp Lys Leu Thr Asn Leu Met Thr His Lys Asp Glu Val
        195                 200                 205

GTA GCG CAC GCG ACT CTA TTG GAC ATA CCA GCC CAA GTA CAA TGG TCA        672
Val Ala His Ala Thr Leu Leu Asp Ile Pro Ala Gln Val Gln Trp Ser
    210                 215                 220

AGA CCA AGA AGG GGA GAC GTG TTG TAACAGAGTA ATCATGTAAT ATTGTATGTA        726
Arg Pro Arg Arg Gly Asp Val Leu
225                 230

AGGTTATGTA TGTTCGTATG GTATGGAAAA AAAAAAAAAA AAAGGATGCT ATGTGGAGAA      786

TGTAAGGCGT GGTAGCTCCG GATAATTCAG TCTGTAGGCT TCATCACGGG CAGTGGCCTG      846

ACTCTGAGAG CTTGCTCCGG TATTAAGTTG TGCGTTTGAA ATTTTCTGGA AAAAAGAAAT      906

TGATTGGTTG AAGCTATACT CGTCGAAAGA TTTCTTCGGC AGTGGTTGTT GCTCCACCTG      966

CACGGGAGTT GTGTTTGCGT TTATGTTCGG CTTGGCTATA TTATTAGCGA GTGATGTTTG     1026

CAATTTGCTG TATTGAGAAT CAATTTGGGT GCGTAAGCTT TCAATAATTT TGCAGACCGC     1086

AGGCACTTCC AACTTTATGA GTTGCAGGTA TTCTCTTTTA TGAATATACG ATGACGACGA     1146

TGACGACGAC GCATCCATGC GCAAAAGCTC AGGGTGTCTA GATAGTTTGT TAGTCAATAA     1206

ATCCACATAT CTAAAATAAT AAATAAACGA CAGCGACAAG TCGTTGGCCT GGAACGCACA     1266

CTGTGCCTTT TCCAATATGC CGATGCATGT TTTCAGGTAA ATTCTCAATG GTATCGCCGG     1326

ATTGAAGCGA TAATCCTTAG CGTCCTGAAC CAATTGCTTA CTAGACTTCA TGACCTACCG     1386

GGGCCAGATA AAGATGCGGA AGGAAGAGAA AAAATGTATA GTGGTTGGTG AACCGCAACA     1446

ATAATTCGTG CCAACACTTT AATCGAAGCA AAAATTGTCT TGTATGTTAT TAATATTATC     1506

TATCTAACCA TTGATTTACG TATAAAACTG TCGATGCTCA TCGCCTAGCA ATGAAAAAAT     1566

TTTTTCTTTT TTTTTTCATT ATTTCTCTTT GTTGCGTACT TTTTTTCATT GCGTTTCGCG     1626

GCAAAAGCGA TTCGAGTTGA CTGGAAGTGT GTTATACTAT AAAAAGTGTA TATGCCTATT     1686

TTTGGTTCTG ATCTTTACTT TACTGTTAAG TACTGGCTGA GGCAGTAGAC TCTGCCTCTG     1746

TTACGGCAGC GGTATTCGCC TCGGCATCAG CAGCCGCCCA CGGTAGAGTA GGTTCTGTTG     1806

TTTTGACGTT TGCCAAGGTA CTGTCCAAAT GCTCCTTCAG CAAGGCCTCA TTACTTTCCT     1866

TCTCCGGACC CACCGATTGC GTGATCTCCT GTACACGGTT CAAGAACTTG TTCAAATTGT     1926

AGCCCGCAGC AGCATCAGAG ACTTCTTGTG TGTAAGGGAC ACCCCTCAAC TCCTTGACTC     1986

TTCTTTTGTG CACTTTGCCC TTTAAATGCG TTTTTAACGC TATAGCAGTC TCCATGTATT     2046

TGGCACAGTG TATGCAATAG TGCTGACCAA GGCCCGGTTT GGTTTCATCC AATGGCTGGT     2106

TCAGAAGCTT CTGTACTGAT TCCTTGGTGG ACAAATCGTT ATAGATCAGG TCCAAGTCTC     2166

GTGTTCTTCT TTTAGTCTTG TATCTCTTCA CCGAATATCT ACCCATGATG CGCTATTGTT     2226

TTATCTTCAC TTGTCTGTGT GTTTAACTGC CTTTCAATTC ACCTCATCTC ATCTCCCGCT     2286
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ACTTTCCATA TATAAAAGCA AAATTAATTT GCTTTTTCCC CTGTCAGTAT AAAAAAATTT 2346

TCCGCAGGAT ATAGAAAAAA AAGAAATGAA ATTATAGTAG CGGTTATTTC CGTGGGGTGC 2406

TTTTTTACAC CTGTACATCT TTTCCCTCCG TACATTTTTT TTATTTTTTT TTTGGGTTTT 2466

TTTTTTTCGA TATTTTTCCC TCCGAAACTA GTTAGCACAA TAATGCTGAC TAAGGAAACT 2526

TTTCATCTCA GAATTGATGG TCAGTTTGGT TTCTCTAGAG AATAGTTTAT AAAAAGATGT 2586

TGATGTGGAG CAACCATTTA TACATCCTTT CCGCAAGTGC TTTTGGAGTG GGACTTTCAA 2646

ACTTTAAAGT ACAGTATATC AAATAACTAA TTCAAGATGG CTAGAAGACC AGCTAGATGT 2706

TACAGATACC AAAAGAACAA GCCTTACCCA AAGTCTAGAT ACAACAGAGC TGTTCCAGAC 2766

TCCAAGATCA GAATCTACGA TTTGGGTAAG AAGAAGGCTA CCGTCGAT 2814

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 232 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Glu Phe Gln Tyr Thr Lys Gln Leu His Phe Pro Val Gly Pro Lys Ser
1 5 10 15

Thr Asn Cys Glu Val Ala Glu Ile Leu Leu His Cys Asp Trp Glu Arg
20 25 30

Tyr Ile Asn Val Leu Ser Ile Thr Arg Thr Pro Asn Val Pro Ser Gly
35 40 45

Thr Ser Phe Ser Thr Arg Thr Arg Tyr Met Phe Arg Trp Asp Asp Gln
50 55 60

Gly Gln Gly Cys Ile Leu Lys Ile Ser Phe Trp Val Asp Trp Asn Ala
65 70 75 80

Ser Ser Trp Ile Lys Pro Met Val Glu Ser Asn Cys Lys Asn Gly Gln
85 90 95

Ile Ser Ala Thr Lys Asp Leu Val Lys Leu Val Glu Glu Phe Val Glu
100 105 110

Lys Tyr Val Glu Leu Ser Lys Glu Lys Ala Asp Thr Leu Lys Pro Leu
115 120 125

Pro Ser Val Thr Ser Phe Gly Ser Pro Arg Lys Val Ala Ala Pro Glu
130 135 140

Leu Ser Met Val Gln Pro Glu Ser Lys Pro Glu Ala Glu Ala Glu Ile
145 150 155 160

Ser Glu Ile Gly Ser Asp Arg Trp Arg Phe Asn Trp Val Asn Ile Ile
165 170 175

Ile Leu Val Leu Leu Val Leu Asn Leu Leu Tyr Leu Met Lys Leu Asn
180 185 190

Lys Lys Met Asp Lys Leu Thr Asn Leu Met Thr His Lys Asp Glu Val
195 200 205

Val Ala His Ala Thr Leu Leu Asp Ile Pro Ala Gln Val Gln Trp Ser
210 215 220

Arg Pro Arg Arg Gly Asp Val Leu
225 230

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1485 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

ATGGACTTAA GAGTAGGAAG GAAATTTCGT ATTGGCAGGA AGATTGGGAG TGGTTCCTTT 60

GGTGACATTT ACCACGGCAC GAACTTAATT AGTGGTGAAG AAGTAGCCAT CAAGCTGGAA 120

TCGATCAGGT CCAGACATCC TCAATTGGAC TATGAGTCCC GCGTCTACAG ATACTTAAGC 180

GGTGGTGTGG GAATCCCGTT CATCAGATGG TTTGGCAGAG AGGGTGAATA TAATGCTATG 240

GTCATCGATC TTCTAGGCCC ATCTTTGGAA GATTTATTCA ACTACTGTCA CAGAAGGTTC 300

TCCTTTAAGA CGGTTATCAT GCTGGCTTTG CAAATGTTTT GCCGTATTCA GTATATACAT 360

GGAAGGTCGT TCATTCATAG AGATATCAAA CCAGACAACT TTTTAATGGG GGTAGGACGC 420

CGTGGTAGCA CCGTTCATGT TATTGATTTC GGTCTATCAA AGAAATACCG AGATTTCAAC 480

ACACATCGTC ATATTCCTTA CAGGGAGAAC AAGTCCTTGA CAGGTACAGC TCGTTATGCA 540

AGTGTCAATA CGCATCTTGG AATAGAGCAA AGTAGAAGAG ATGACTTAGA ATCACTAGGT 600

TATGTCTTGA TCTATTTTTG TAAGGGTTCT TTGCCATGGC AGGGTTTGAA AGCAACCACC 660

AAGAAACAAA AGTATGATCG TATCATGGAA AAGAAATTAA ACGTTAGCGT GGAAACTCTA 720

TGTTCAGGTT TACCATTAGA GTTTCAAGAA TATATGGCTT ACTGTAAGAA TTTGAAATTC 780

GATGAGAAGC CAGATTATTT GTTCTTGGCA AGGCTGTTTA AAGATCTGAG TATTAAACTA 840

GAGTATCACA ACGACCACTT GTTCGATTGG ACAATGTTGC GTTACACAAA GGCGATGGTG 900

GAGAAGCAAA GGGACCTCCT CATCGAAAAA GGTGATTTGA ACGCAAATAG CAATGCAGCA 960

AGTGCAAGTA ACAGCACAGA CAACAAGTCT GAAACTTTCA ACAAGATTAA ACTGTTAGCC 1020

ATGAAGAAAT TCCCCACCCA TTTCCACTAT TACAAGAATG AAGACAAACA TAATCCTTCA 1080

CCAGAAGAGA TCAAACAACA AACTATCTTG AATAATAATG CAGCCTCTTC TTTACCAGAG 1140

GAATTATTGA ACGCACTAGA TAAAGGTATG GAAAACTTGA GACAACAGCA GCCGCAGCAG 1200

CAGGTCCAAA GTTCGCAGCC ACAACCACAG CCCCAACAGC TACAGCAGCA ACCAAATGGC 1260

CAAAGACCAA ATTATTATCC TGAACCGTTA CTACAGCAGC AACAAAGAGA TTCTCAGGAG 1320

CAACAGCAGC AAGTTCCGAT GGCTACAACC AGGGCTACTC AGTATCCCCC ACAAATAAAC 1380

AGCAATAATT TTAATACTAA TCAAGCATCT GTACCTCCAC AAATGAGATC TAATCCACAA 1440

CAGCCGCCTC AAGATAAACC AGCTGGCCAG TCAATTTGGT TGTAA 1485

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

CCTACTCTTA GGCCCGGGTC TTTTTAATGT ATCC 34

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

GGAATCACTA CAGGGATG 18

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 543 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GATCTCTGAA TTGAAGAACC GTTCAAACAT TGGCGAGCCC TTAACCAAAT CTTCCAATGA 60

AAGTACTTAT AAAGACATTA AAGCCACCGG CAATGATGGT GATCCGAATT TGGCTCTAAT 120

GAGAGCGGAG AATCGAGTAT TAAAATATAA ACTAGAGAAT TGTGAAAAAC TACTAGATAA 180

AGATGTGGTT GATTTGCAAG ATTCTGAGAT TATGGAAATT GTAGAAATGC TTCCCTTTGA 240

GGTCGGCACC CTTTTGGAAA CAAAGTTCCA AGGTTTGGAA TCACAAATAA GGCAATATAG 300

GAAATACACT CAAAAACTTG AAGACAAGAT CATGGCGCTA GAAAAAAGTG GTCATACTGC 360

AATGTCGCTA ACTGGGTGTG ACGGCACTGA AGTGATCGAA TTACAGAAGA TGCTCGAGAG 420

GAAGGATAAA ATGATTGAGG CCCTGCAGAG TGCCAAACGA CTGCGGGATA GGGCTTTGAA 480

ACCACTCATT AATACACAGC AATCACCGCA CCCTGTCGTG GATAACGATA AATGATTAGG 540

TGA 543

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 35 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

CCTTCCTACT CTTAAGCCCG GGCCGCAGGA ATTCG 35

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

AGCAATATAG GATCCTTACA ACCAAATTGA 30

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

CCTACTCTTA AGCCCGGGTC TTTTTAATGT ATCC 34

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

GTCTCAAGTT TTGGGATCCT TAATCTAGTG CG 32

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 32 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

CACCATCGCC CCCGGGTAAC GCAACATTGT CC 32

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3628 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GATCAGATGA TATAGCTTTT TGTGTGCCGT ACCTTTCCGC GATTCTGCCC GTATATCTTG 60

GTCCCTGAGC TATTTTCTGA GATTCTTTTT GTTGCTTTGC CAAATCATTG GCGTCATTCA 120

TGGTCATACC AAATCCCAAT TTGGCAAACT TGGGTGTTAA AGTATCTTGC TGTTCTTTTC 180

TAGTTGTGTC GAAGCTGTTT GAAGTGTCAT TTAAAAAATC ATTGAATTCA TCAGGCTGGG 240

TATTAATATC ATCTATACTG TTATTATTGT TGCCTTTACT GTTATTCATA AATTGGGAAT 300

CGTAATCATT TGTCTAATTT TGGTGCTAGA AGACGAATTA GTGAACTCGT CCTCCTTTTC 360

TTGTTGAGCC TCTTTTTTAA ATTGATCAAA CAAGTCTTCT GCCTGTGATT TGTCGACTTT 420

CTTTGCGGTT AGTCTAGTGG GCTTTCTTGA CGAAGACAAA ATTGAATGTT TCTTTTTATC 480

TTGCGAGTTT AATACCGGTT TCTTTCTGCA TGCCGTTAAG ATGGAACTTC TCGTTTTAGT 540

GACAGTGGTC TTGGGTGTGC TGCCTGTGGT GTTGTTTTTT GGGGCGAGAG AGCCTGTATT 600

TACATTGAGT TTAGAACTGG AATTGGAGCT TGGTTTTTGC CAATTAGAGA AAAAATCGTC 660

AACACTATTT TCTTTGGAAG TCGACCTGGA AGCGTCTGAA TCGGTGTCCA ACGGTGAGTC 720

CGAAGAATCT TGACCGTTCA AGACTAATTC TGATGGGTAT AACTCCATAT CCTTTTGAAC 780

CTTCTTGTCG AGATGTATCT TATATTTCTT AGCAACAGGG CTCGTATATT TTGTTTTCGC 840

GTCAACATTT GCTGTATTTA GTAGCTGTTT CCCATTGTTC TTTAAGAAAA AATCACGAGC 900

CTTATGGTTC CCACCCAACT TAAACCTTCT TAAATTGTTA ATTGTCCATT TATCTAATGT 960

AGAAGACTTT ACAAAGGTGA TATGAACACC CATGTTTCTA TGCACAGCAG AGCATTGAAT 1020

ACACAGCATC ACACCAAAAG GTACCGAAGT CCAGTAGGAT TCTTGTTACC ACAATCAAAA 1080

CAAACTCGAT TTTCCATGTT GCTACCTAGC TTCTGAAAAA CTTGTTGAGT AGTCTGTTCC 1140

GTGGCAAATG TTTCTCCTTC ATCGTTACTC ATTGTCGCTA TGTGTATACT AAATTGCTCA 1200

AGAAGACCGG ATCAACAAGT ACTTAACAAA TACCCTTTCT TTGCTATCGC CTTGATCTCC 1260

TTTTATAAAA TGCCAGCTAA ATCGTGTTTA CGAAGAATAG TTGTTTTCTT TTTTTTTTTT 1320

TTTTTTCGAA ACTTTACCGT GTCGTCGAAA ATGACCAAAC GATGTTACTT TTCCTTTTGT 1380

GTCATAGATA ATACCAATAT TGAAAGTAAA ATTTTAAACA TTCTATAGGT GAATTGAAAA 1440

GGGCAGCTTA GAGAGTAACA GGGGAACAGC ATTCGTAACA TCTAGGTACT GGTATTATTT 1500

GCTGTTTTTT AAAAAAGAAG GAAATCCGTT TTGCAAGAAT TGTCTGCTAT TTAAGGGTAT 1560

ACGTGCTACG GTCCACTAAT CAAAAGTGGT ATCTCATTCT GAAGAAAAAG TGTAAAAAGG 1620

ACGATAAGGA AAGATGTCCC AACGATCTTC ACAACACATT GTAGGTATTC ATTATGCTGT 1680

AGGACCTAAG ATTGGCGAAG GGTCTTTCGG AGTAATATTT GAGGGAGAGA ACATTCTTCA 1740

TTCTTGTCAA GCGCAGACCG GTAGCAAGAG GGACTCTAGT ATAATAATGG CGAACGAGCC 1800

AGTCGCAATT AAATTCGAAC CGCGACATTC GGACGCACCC CAGTTGCGTG ACGAATTTAG 1860

AGCCTATAGG ATATTGAATG GCTGCGTTGG AATTCCCCAT GCTTATTATT TTGGTCAAGA 1920

AGGTATGCAC AACATCTTGA TTATCGATTT ACTAGGGCCA TCATTGGAAG ATCTCTTTGA 1980

GTGGTGTGGT AGAAAATTTT CAGTGAAAAC AACCTGTATG GTTGCCAAGC AAATGATTGA 2040

TAGAGTTAGA GCAATTCATG ATCACGACTT AATCTATCGC GATATTAAAC CCGATAACTT 2100

TTTAATTTCT CAATATCAAA GAATTTCACC TGAAGGAAAA GTCATTAAAT CATGTGCCTC 2160

CTCTTCTAAT AATGATCCCA ATTTAATATA CATGGTTGAC TTTGGTATGG CAAAACAATA 2220

TAGAGATCCA AGAACGAAAC AACATATACC ATACCGTGAA CGAAAATCAT TGAGCGGTAC 2280

CGCCAGATAT ATGTCTATTA ATACTCATTT TGGAAGAGAA CAGTCACGTA GGGATGATTT 2340

AGAATCGCTA GGTCACGTTT TTTTTTATTT CTTGAGGGGA TCCTTGCCAT GGCAAGGTTT 2400

GAAAGCACCA AACAACAAAC TGAAGTATGA AAAGATTGGT ATGACTAAAC AGAAATTGAA 2460

TCCTGATGAT CTTTTATTGA ATAATGCTAT TCCTTATCAG TTTGCCACAT ATTTAAAATA 2520

TGCACGTTCC TTGAAGTTCG ACGAAGATCC GGATTATGAC TATTTAATCT CGTTAATGGA 2580

TGACGCTTTG AGATTAAACG ACTTAAAGGA TGATGGACAC TATGACTGGA TGGATTTGAA 2640

TGGTGGTAAA GGCTGGAATA TCAAGATTAA TAGAAGAGCT AACTTGCATG GTTACGGAAA 2700

TCCAAATCCA AGAGTCAATG GCAATACTGC AAGAAACAAT GTGAATACGA ATTCAAAGAC 2760

ACGAAATACA ACGCCAGTTG GGACACCTAA GCAACAAGCT CAAAACAGTT ATAACAAGGA 2820

CAATTCGAAA TCCAGAATTT CTTCGAACCC GCAGAGCTTT ACTAAACAAC AACACGTCTT 2880

GAAAAAAATC GAACCCAATA GTAAATATAT TCCTGAAACA CATTCAAATC TTCAACGGCC 2940

AATTAAAAGT CAAAGTCAAA CGTACGACTC CATCAGTCAT ACACAAAATT CACCATTTGT 3000

ACCATATTCA AGTTCTAAAG CTAACCCTAA AAGAAGTAAT AATGAGCACA ACTTACCAAA 3060

CCACTACACA AACCTTGCAA ATAAGAATAT CAATTATCAA AGTCAACGAA ATTACGAACA 3120

AGAAAATGAT GCTTATTCTG ATGACGAGAA TGATACATTT TGTTCTAAAA TATACAAATA 3180

TTGTTGTTGC TGTTTTTGTT GCTGTTGATA AAGCGATTTT TATACTTTTC TCTTTTTCCT 3240

TTTTTTTTTT GATTGGCTGT TTCCTTATGC CGCTCTTTCC CAATTTATGA CTTTCCAATA 3300

ATGTATTATT TTGTTTCTCT TTCTCTCTGT TACCCTTTAT TTTATCATCT ACAATAATTG 3360

AATTCCGGAG AGGGTAAAGA AACAGGAAAA AGAAGAAAAT GAGACATAGT CAGCATCGTA 3420

ATCGTTTTCC TTCTGTATAT TCCTTTATCA AAAGACTACA CGCACATATA TATTAATCCC 3480

GGTATGTTTT TGGTGTGCTA AATCTATCTT CAAGCACTAT TATAGCATTT TTTTAAGAAT 3540

ATCCAAAATA ATATGTAATT TATGATTAAT CAAGGTTCAA GAATTGGAGA AACCGTGAGC 3600

GACTTCTTTG ATACTTGGAT GTAAGCTT 3628

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

TGAAGATCGT TGGCCCGGGT TTCCTTATCG TCC 33

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2468 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

AATATTTCAA GCTATACCAA GCATACAATC AACTCCAAGC TTCGAGCGGC CGCCAGTGTG 60

CTCTAAAGGA AAAAGCGAGT GCCTTTAGCC TTAAAAGCGT TATAATATTA TTATGGCTTT 120

GGACCTCCGG ATTGGGAACA AGTATCGCAT TGGTCGTAAA ATTGGCAGTG GATCTTTCGG 180

AGACATTTAT CTTGGGACTA ATGTCGTTTC TGGTGAAGAG GTCGCTATCA AGCTAGAATC 240

AACTCGTGCT AAACACCCTC AATTGGAGTA TGAATACAGA GTTTATCGCA TTTTGTCAGG 300

AGGGGTCGGA ATCCCGTTTG TTCGTTGGTT CGGTGTAGAA TGTGATTACA ACGCTATGGT 360

GATGGATTTA TTGGGTCCTT CGTTGGAAGA CTTGTTTAAT TTTTGCAATC GAAAGTTTTC 420

TTTGAAAACA GTTCTTCTCC TTGCGGACCA GCTCATTTCT CGAATTGAAT TCATTCATTC 480

AAAATCTTTT CTTCATCGTG ATATTAAGCC TGATAACTTT TTAATGGGAA TAGGTAAAAG 540

AGGAAATCAA GTTAACATAA TTGATTTCGG ATTGGCTAAG AAGTATCGTG ATCACAAAAC 600

TCACCTGCAC ATTCCTTATC GCGAGAACAA GAATCTTACA GGTACTGCAC GCTATGCTAG 660

CATCAATACT CATTTAGGTA TTGAACAATC CCGCCGTGAT GACCTCGAAT CTTTAGGTTA 720

TGTGCTCGTC TACTTTTGTC GTGGTAGCCT GCCTTGGCAG GGATTGAAGG CTACCACGAA 780

AAAGCAAAAG TATGAAAAGA TTATGGAGAA GAAGATCTCT ACGCCTACAG AGGTCTTATG 840

TCGGGGATTC CCTCAGGAGT TCTCAATTTA TCTCAATTAC ACGAGATCTT TACGTTTCGA 900

TGACAAACCT GATTACGCCT ACCTTCGCAA GCTTTTCCGA GATCTTTTTT GTCGGCAATC 960

TTATGAGTTT GACTATATGT TTGATTGGAC CTTGAAGAGA AAGACTCAAC AAGACCAACA 1020

ACATCAGCAG CAATTACAGC AACAACTGTC TGCAACTCCT CAAGCTATTA ATCCGCCGCC 1080

AGAGAGGTCT TCATTTAGAA ATTATCAAAA ACAAAACTTT GATGAAAAAG GCGGAGACAT 1140

TAATACAACC GTTCCTGTTA TAAATGATCC ATCTGCAACC GGAGCTCAAT ATATCAACAG 1200

ACCTAATTGA TTAGCCTTTC ATATTATTAT TATATAGCAT GGGCACATTA TTTTTATATT 1260

TTCTTCTCAT CTGGAGTCTT CCAATACTTG CCTTTTATCC TCCAGACGTC CTTTAATTTT 1320

GTTGATAGCG CAGGGCTTTT TCCTTGGGAT GGCGAAAGTT ACTTTGCTTA TAGTTTATTG 1380

AGGGTTCATA GCTTATTTGG CTGAAGATCT TGTGTTGACT TAAATTCTAT GCTAACCTCA 1440

TGATCATATC CTCATTATGG CAAGTTTTGG TGAAAAATTT TTTAATATTA GTACATTTGC 1500

TAATAATACA TTTGGTATTT GTTTTTACTA CCTGTGAATC TATTCATACA TTATCATATA 1560

TGTTTCGAGC CAGGAACAGA AAAAAGTGAG AGAATTTTCT GCAGAAATGA TCATAATTTT 1620

ATCTTCGCTT AACACGAATC CTGGTGACAG ATTATCGTGG TTTAAAGCCT TTTTTTTACG 1680

ACGCCATAAG CAAATTGGTT ACTTTTTTAT GTGTGATGAG CCTTGGGGTT TAATCTAATT 1740

AGAAGGCATT GCATTCATAT ACTTTTAATA ATATATTATC AGCTATTTGC TGCTTTTCTT 1800

TATAGATACC GTCTTTTCCA AGCTGAACTC ATTTAATCAG CGTCGTTTAA CCTTAGGATG 1860

CTTAAGATGC GTTTAAATTC AATGACTTAA TGCTCGAGGG ATGAATGGTT TGTTTTAGTT 1920

CGTGTTCTGG GTGCATGATC TCGTGCTTGA CTGTTTTATT GAAGCGTTCA TTTCATGAAG 1980

TGTCTTTCGA TGTTGTTCAC ACTTCTGTTT GCTAAATATA ATAAATATTT TGCTTTTCAC 2040

TTTAGAGCAC ACTGGCGGCC GCTCGAAGCT TTGGACTTCT TCGCCATTGG TCAAGTCTCC 2100

AATCAAGGTT GTCGGCTTGT CTACCTTGCC AGAAATTTAC GAAAAGATGG AAAAGGGATC 2160

CAAATCGTTG GTAGATACTT GTTGACACTT CTAAATAAGC GAATTTCTTA TGATTTATGA 2220

TTTTTATTAT TAAATAAGTT ATAAAAAAAA TAAGGTATAC AAATTTTAAA GTGACTCTTA 2280

GGTTTTAAAA CGAAAATTCT TATTCTTGAG TAACTCTTTC CTGTAGGTCA GGTTGCTTTC 2340

TCAGGTATAG CATGAGGTCG CTCTTATTGA CCACACCTCT ACCGGCATGC CGAGCAAATG 2400

CCTGCAAATC GCTCCCCATT TCACCCAATT GTAGATATGC TAACTCCAGC AATGAGCCGA 2460

TGAATCTC 2468

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

GGGTTATAAT ATTATCCCGG GTTTGGACCT CCGG 34

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

TCCCTCTCTA GATATGGCGA GATAGTTA 28

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

GTTTACACTC GAGGCATATA GTGATACA 28

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5093 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GCTAGCTTTT GCCGGGGAAC CCATCCCGAA AAAATTGCAA AAAAAAAAAT AGCCGCCGAC 60

CGTTGGTCGC TATTCACGGA ATGATAGAAA AATAGCCGCG CTGCTCGTCC TGGGTGACCT 120

TTTGTATATT GTATAAAGAT AAACATAGTG CTATCAGGAA TATCTTTATA TACACACGCA 180

TACTGAATGT GGTTGAAGTT CAAAAAATAT CACAAACGTT AAGAAGTTTT ACTGGTAAAC 240

ATATAGACAT AGTGGAGCGC TTGCTCGAGG TCAAATGCAG ACGGATACGA GAGCGCGGGA 300

GGGAAACCGG AGAAGGTCAA TATGCCCATA ATTCTTCTTC TTTGAGGTTG GCAATTATAT 360

ATTGTATCTG AATTAGGCAA ATAGAAAAGA GACCTTACCA TTAGCGCCAT CGTAGAGTCC 420

CATTTCACCT TTTCTTAGTT CTTTATATAT GTCTGCGTAT GGCCCACATA TGCGCGCACA 480

GTGCGCGCCA CCCTCTAAGA ACGATAAACA TAAAATAAAC ACATAAACAA TCAACGACAG 540

TTCGCGCTTC CCTCACTAAA TATGGCGAGA TAGTTAAACA ATCATGGCTC GTTCTTCCTT 600

GCCCAACCGC CGCACCGCCC AGTTCGAAGC GAACAAGAGG AGGACCATTG CACATGCTCC 660

ATCTCCAAGT CTTTCAAATG GGATGCACAC TCTAACGCCG CCCACCTGTA ACAATGGTGC 720

TGCCACTTCA GACTCCAATA TACATGTATA TGTAAGGTGC AGATCGCGTA ATAAGCGAGA 780

AATAGAGGAA AAAAGTAGTG TAGTTATATC TACACTAGGC CCACAAGGGA AAGAAATCAT 840

TCTGTCCAAC GGTTCTCACC AATCGTATTC GTCCTCGAAG AAAACTTACC AATTTGATCA 900

GGTGTTCGGC GCAGAATCTG ACCAGGAAAC AGTGTTTAAT GCCACTGCAA AAAACTACAT 960

TAAGGAAATG TTGCACGGGT ACAATTGTAC AATATTTGCA TACGGTCAAA CGGGAACAGG 1020

TAAAACCTAC ACTATGTCTG GCGATATAAA TATTCTCGGT GATGTGCAAT CTACCGATAA 1080

TCTATTATTA GGAGAGCATG CAGGTATCAT ACCACGGGTT CTGGTCGATT TGTTTAAAGA 1140

ATTGAGCTCC TTAAATAAAG AGTACTCCGT AAAAATATCC TTTTTAGAGT TGTACAATGA 1200

AAATTTGAAA GATCTGCTCT CTGATAGTGA GGACGATGAT CCTGCAGTCA ACGATCCCAA 1260

GAGGCAGATT CGTATTTTTG ACAATAACAA CAATAATTCA TCCATCATGG TCAAGGGGAT 1320

GCAGGAAATC TTTATTAACT CTGCACACGA AGGCTTGAAT TTGCTAATGC AGGGTTCGTT 1380

AAAAAGGAAA GTGGCCGCTA CTAAATGCAA CGATCTTTCA TCAAGGTCTC ACACCGTCTT 1440

TACAATCACA ACAAACATAG TTGAGCAAGA TAGCAAAGAC CATGGACAAA ACAAAAATTT 1500

TGTTAAAATT GGCAAATTGA ATTTGGTGGA TTTGGCAGGC AGTGAAAACA TCAACAGATC 1560

GGGTGCGGAG AATAAAAGGG CTCAAGAAGC TGGCCTAATA AACAAATCGC TGCTAACACT 1620

AGGCCGTGTT ATCAACGCAC TCGTTGATCA TTCTAACCAT ATACCTTACA GAGAATCTAA 1680

GCTAACAAGA TTGCTACAAG ACTCTTTAGG TGGTATGACG AAAACATGCA TTATCGCAAC 1740

TATATCACCT GCGAAAATAT CCATGGAAGA GACTGCAAGT ACGCTAGAAT ATGCAACGAG 1800

AGCCAAATCA ATTAAGAATA CTCCACAAGT AAATCAGTCT TTATCGAAGG ATACATGTCT 1860

CAAAGACTAC ATTCAAGAGA TTGAAAAATT AAGAAATGAT TTGAAAAATT CAAGAAACAA 1920

ACAAGGTATA TTTATAACTC AAGATCAGTT GGACCTTTAC GAGAGCAATT CTATCTTGAT 1980

TGATGAGCAA AATCTAAAAA TACATAACCT GCGAGAACAA ATTAAAAAAT TCAAAGAAAA 2040

CTACCTGAAC CAATTAGATA TCAATAATCT TTTACAGTCT GAAAAGGAAA AACTAATTGC 2100

CATAATACAG AATTTTAATG TCGATTTTTC TAACTTTTAC TCGGAAATCC AAAAAATTCA 2160

CCATACTAAT CTCGAACTAA TGAATGAAGT CATACAACAG AGAGATTTTT CACTAGAAAA 2220

TTCTCAAAAA CAGTATAATA CGAACCAGAA CATGCAATTA AAAATCTCTC AACAAGTTTT 2280

ACAGACTTTG AACACTTTAC AGGGCTCTTT AAATAATTAT AACTCTAAAT GTTCCGAAGT 2340

TATCAAAGGC GTCACCGAAG AACTAACCAG GAACGTAAAT ACCCATAAGG CGAAACACGA 2400

TTCTACTCTC AAATCGTTAT TAAACATTAC TACTAACTTA TTGATGAATC AGATGAACGA 2460

ACTGGTGCGT AGTATTTCGA CTTCATTGGA AATATTTCAG AGTGATTCTA CTTCTCACTA 2520

TCGTAAAGAT TTGAATGAAA TCTACCAATC ACATCAACAA TTTCTAAAAA ATTTACAAAA 2580

CGATATTAAA AGCTGTCTTG ATTCGATAGG CAGTTCAATT CTAACTTCCA TAAACGAAAT 2640

ATCGCAAAAT TGCACCACTA ACTTGAATAG TATGAATGTT TTAATAGAAA ACCAGCAGTC 2700

AGGATCATCG AAATTAATTA AAGAGCAAGA TTTAGAAATA AAAAAACTGA AAAACGATCT 2760

GATCAATGAG CGCAGGATTT CTAACCAATT CAACCAACAG TTGGCTGAAA TGAAGCGATA 2820

TTTTCAGGAT CACGTTTCCA GGACGCGTAG TGAATTCCAC GACGAACTTA ACAAATGTAT 2880

CGATAACCTA AAAGATAAAC AATCTAAGTT GGATCAAGAT ATCTGGCAGA AGACGGCCTC 2940

TATTTTCAAC GAAACAGATA TCGTAGTTAA TAAAATTCAT TCCGACTCAA TAGCATCCCT 3000

CGCTCATAAT GCTGAAAACA CTTTGAAAAC GGTTTCTCAG AACAATGAAA GCTTTACTAA 3060

CGATTTAATC AGTCTATCAC GCGGAATGAA CATGGACATA TCCTCCAAAC TGAGAAGTTT 3120

GCCCATCAAT GAATTTTTAA ACAAGATATC ACAAACCATT TGTGAAACCT GTGGCGATGA 3180

TAACACAATC GCATCAAATC CAGTATTGAC CTCTATTAAA AAATTTCAAA ATATAATTTG 3240

TTCAGACATT GCCCTAACAA ATGAGAAGAT CATGTCATTA ATAGATGAAA TACAATCACA 3300

AATTGAAACC ATATCTAATG AAAACAATAT CAATTTGATT GCAATAAATG AAAATTTTAA 3360

TTCTTTGTGC AATTTTATAT TAACTGATTA CGATGAGAAT ATTATGCAAA TCTCAAAAAC 3420

ACAAGATGAG GTGCTTTCTG AACATTGCGA GAAGCTACAA TCACTGAAAA TACTGGGTAT 3480

GGACATTTTC ACTGCTCACA GCATAGAAAA ACCCCTTCAT GAGCATACAA GACCTGAAGC 3540

GTCAGTAATC AAGGCTTTAC CCTTATTGGA TTATCCAAAA CAATTTCAGA TTTATAGGGA 3600

TGCTGAAAAT AAGAGCAAAG ACGACACATC TAATTCTCGT ACTTGTATAC CAAACTTGTC 3660

AACTAATGAA AATTTTCCTC TTTCACAATT CAGTCCAAAA ACCCCAGTGC CAGTGCCTGA 3720

TCAACCTCTA CCAAAAGTTC TTATACCGAA AAGCATAAAC TCGGCCAAGT CCAATAGATC 3780

AAAGACCTTA CCAAATACAG AGGGTACTGG ACGAGAATCG CAGAACAATT TGAAGAGAAG 3840

ATTTACCACC GAGCCAATAT TGAAGGGAGA AGAAACTGAA AATAATGACA TACTGCAAAA 3900

TAAAAAACTT CATCAATAAG GGGATATAGC CATTGTAAAA TATTTGTATC ACTATATGCA 3960

TTGAGTGTAA ACTGTTGCAC CTATAAAGAA TGAAAACAAT CTAGTATGTG TACTTACATA 4020

ATTACACAGT CTTTTTTTTT TTTACCTTGT TTATCCTTCT TGTTCTTCAA GCTTGTAGGT 4080

TTTTTTGACT CAGTTTTTAC TGCAGGAAAA TCTTTACGAA TCATGTTTGA ACTGCCCATA 4140

TTTGATAAAC TAACTTCTTG CTTTGCTGCC ATCGACTGCT CAGCAACTTC CCTTGACATT 4200

CCCTTTGCTG AGGAAGAACT TTTCCTGATG CTTGTATCAG AACCCGTTTT AATACCATTT 4260

CTATTCGTGT TTGAATTCAT GTTAATTTGC AAACCTTGTG GCTCACGATC ACGTTTTGGA 4320

TTTCCAGTAA AGAATGTTTC AGATTTTGAA GAAACTCTTG AATTTGACCC TACGTTACTT 4380

GTTTGACTGT CCACAGTAGA GAATAAATTC AAAGTACTGA TACTTTTATT TTTTTTATGC 4440

TGTTTTTTAC CAATGCTGGC TAGTCCACCG TCCCTTGAGC GTAGCTTATT AATCGCCCTC 4500

TTGTCCTCGT TCCCTGCAGC TTTCTCGTAC CATTTCCATG CGTATTCCAT GTTACGATCA 4560

CAGCCCTTGC CATGCTCATA GAAGTAGCCC AGAGTGAATT GGGCCTTTGG CAAACCAGCA 4620

TTAGCTGCAC GCAAGGCCCA TTGAAAAGCC TCATTTTCAT CTTTTTCAAA AGCAGGTTCT 4680

GCTCCCAGTA AGTACCATGC ACATAAACCT AACATTGCCA CAGAATCGCC TTTTAACGCT 4740

GCCTGCGTAT AATAGTGTAC AGAAAGTGAT GTATCCTGCC CTACTGTATC ATTACCTGTT 4800

TCATAAATCT GTGCCAACAA AGTTGCTGAA GGAACATGCC CTAAACTTGC TGCTTGAATA 4860

TATAGTTCCA TTGCATACTT TTCATCCGGA ATGACAACAT CTAAGAACCC TTCATGATAA 4920

ATCTTAGCCA ATTCGTATGG TGCTGCGGCC GTCAACTCAT TAGCTCTTGC TGCAGCCCTT 4980

GATAACCATT TTACCCCATT TAATTTAGTA TTAACGTCGG TTGGAAGACC CATTCTGCCG 5040

TAGAATGAAT AAAGTCCCAA TTTATACATT GCTGAGGGAT GATTCCTGCT AGC 5093

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

GATAGTTAAG GATCCATGGC TCGTTCTTCC TTGCCCAACC GC 42

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

AAACTTCATC AATGCGGCCG CTAAGGGGAT CCAGCCATTG TAAAT 45

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

TTTCCTTGTT TATCCTTTTC CAA 23

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

GATCACTTCG GATCCGTCAC ACCCAGTTAG 30

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2870 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

AATTTCCTTG TTTATCCTTT TCCAATAGCG GAACAATTGA TAATAAAGCA ATGTAAGCAG 60

AAGCGAAAAA TAAAAAGAAA TAGGCTGCAG AGATTCACAG GCTGCGCTCT AGAAACATTT 120

GAAATCAAGG CAAACATAGA ACACTTGATA AAATTCTTAC CATAATACCA CCATTGATGA 180

TTCAAAAAAT GAGCCCAAGC TTAAGGAGGC CATCAACGAG GTCTAGTTCT GGTTCAAGTA 240

ATATCCCACA ATCGCCCTCT GTACGATCAA CTTCATCGTT TTCTAATCTG ACAAGAAACT 300

CCATACGGAG CACCTCTAAT TCGGGTTCTC AGTCGATTTC TGCATCTTCC ACTAGAAGTA 360

ACTCCCCACT AAGATCCGTA TCAGCCAAAT CCGATCCCTT CCTTCACCCA GGTAGGATAA 420

GGATCAGGCG GAGCGACAGT ATTAACAACA ACTCGAGAAA AAACGATACA TATACTGGGT 480

CAATCACTGT GACCATCCGG CCGAAACCAC GGAGCGTTGG AACTTCCCGT GACCATGTGG 540

GGCTAAAATC GCCCAGGTAC TCTCAACCAA GATCCAACTC ACATCACGGT AGCAATACAT 600

TTGTTAGAGA CCCCTGGTTT ATTACTAATG ACAAAACAAT AGTGCATGAA GAAATTGGAG 660

AGTTCAAGTT CGATCATGTT TTTGCTTCCC ATTGCACTAA TTTGGAAGTT TATGAAAGAA 720

CCAGTAAACC AATGATTGAT AAGTTATTGA TGGGGTTTAA TGCCACCATA TTTGCGTACG 780

GTATGACCGG GTCAGGTAAA ACGTTTACAA TGAGCGGAAA TGAACAAGAG CTAGGCCTAA 840

TTCCTTTATC TGTGTCGTAT TTATTTACCA ATATCATGGA ACAATCAATG AATGGCGATA 900

AAAAGTTCGA CGTTATAATA TCGTACCTCG AAATTTACAA TGAAAGGATT TACGACCTGT 960

TAGAAAGCGG ATTAGAAGAA TCCGGTAGTA GAATCAGTAC TCCTTCAAGG TTATATATGA 1020

GCAAGAGCAA CAGCAATGGA TTGGGCGTAG AATTAAAAAT CAGAGATGAC TCTCAGTATG 1080

GGGTCAAAGT TATCGGTCTC ACCGAAAGAA GATGTGAAAG TAGTGAAGAA TTATTGAGGT 1140

GGATTGCAGT TGGTGACAAA AGTAGGAAAA TTGGCGAAAC TGACTACAAT GCAAGAAGCT 1200

CACGATCTCA TGCCATTGTA CTGATTCGTT TAACAAGTAC TAACGTAAAG AACGGCACCT 1260

CAAGATCGAG TACATTGTCG TTGTGTGACC TAGCAGGTTC GGAAAGGGCT ACGGGGCAAC 1320

AAGAGAGGAG AAAGGAAGGT TCATTCATCA ACAAATCCTT ACTTGCTTTG GGGACTGTGA 1380

TATCCAAACT CAGTGCCGAC AAGATGAACT CAGTAGGCTC AAACATTCCC TCGCCATCTG 1440

CAAGTGGCAG TAGCAGCAGT AGTGGAAATG CTACCAATAA CGGCACTAGC CCAAGCAACC 1500

ACATTCCATA TCGTGATTCT AAATTGACTA GATTATTGCA GCCGGCACTA AGCGGTGACA 1560

GCATAGTGAC AACGATATGT ACAGTCGACA CCAGAAATGA TGCGGCAGCG GAAACTATGA 1620

ATACGCTGAG GTTTGCATCA AGAGCGAAAA ACGTCGCACT TCATGTATCC AAAAAATCCA 1680

TCATCAGTAA CGGGAATAAC GATGGAGATA AAGATCGCAC CATTGAGCTA CTGAGACGCC 1740

AATTGGAAGA ACAACGTAGG ATGATCTCTG AATTGAAGAA CCGTTCAAAC ATTGGCGAGC 1800

CCTTAACCAA ATCTTCCAAT GAAAGTACTT ATAAAGACAT TAAAGCCACC GGCAATGATG 1860

GTGATCCGAA TTTGGCTCTA ATGAGAGCGG AGAATCGAGT ATTAAAATAT AAACTAGAGA 1920

ATTGTGAAAA ACTACTAGAT AAAGATGTGG TTGATTTGCA AGATTCTGAG ATTATGGAAA 1980

TTGTAGAAAT GCTTCCCTTT GAGGTCGGCA CCCTTTTGGA AACAAAGTTC CAAGGTTTGG 2040

AATCACAAAT AAGGCAATAT AGGAAATACA CTCAAAAACT TGAAGACAAG ATCATGGCGC 2100

TAGAAAAAAG TGGTCATACT GCAATGTCGC TAACTGGGTG TGACGGCACT GAAGTGATCG 2160

AATTACAGAA GATGCTCGAG AGGAAGGATA AAATGATTGA GGCCCTGCAG AGTGCCAAAC 2220

GACTGCGGGA TAGGGCTTTG AAACCACTCA TTAATACACA GCAATCACCG CACCCTGTCG 2280

TGGATAACGA TAAATGATTA GGTGAGGGTC CCAGATCTCG GGTGCTTTTT TCCTTGTGCG 2340

GATTGTTCTG TAGACTGCGC CTCCGCTTCC CGGCCTTGCT TGAACGGGAT CTATTCTCAG 2400

AAGACAGCGC ATAAAAGGCA GTTTTTAGGC ACTTCTCGTT AAGAAAATAC ACAAATAATG 2460

GATTTACAGT TCGTTTCAGT GTGGTACCAA AAAATTTCAT CAGCTAATAA AGATCAAGAA 2520

GTTTTGGGGT TGTTTCGAGT CTGTCTCGGC CTTAATTGTG CAGGTACTAA AGGAATTAAT 2580

ATATAAAGAT TGTTAAGGCC AAGTGACTGA AACTTGCAAA CGTCTTTGAA TCAGGCTTAT 2640

CTCTTAAATA CTTATATATA TGTTCTTTTA TAGACTTCAT AATCTCTTGT TCCAAGAACA 2700

GTAAAGAGCA ATTAAAAAAA GGAAAATAAC AGTTAAAGAT GATAGCGGAT TCATCAGTTT 2760

TGAAAAAGCA CACAGCAATC AAGAGAAGTA CGAGAATAAT ATCGCTAACA CTCGTTTTGC 2820

TTGGCGTATT TAGCTTCTTA CTACTTACAT GGAATGACTC CTTGGAATTC 2870

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

ACCATAATAC CAGGATCCAT GATTCAAAAA 30

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

CCTGTCGTGG ATAGCGGCCG CTAGGATCCT GAGGGTCCCA GA 42

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

ACATCATCTA GAGACTTCCT TTGTGACC 28

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

TATATAATCG ATTGAAAGGC AATATC 26

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3883 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

AGCAAGAATT GAACATGGAT GAATTCATTG GATCAAAGAC CGATTTAATC AAAGATCAAG 60

TGAGAGATAT TCTTGATAAA TTGAATATTA TTTAATTCTT CATTTAGAAA AATTTCAGCT 120

GCTTTTTTTT TTCTTTTTCT TTCCTTAGGC GTCTCGAGGT TACAAGTCGG AGTCCCTCTT 180

CACTATCGTT TGTCCACTTT TTTTATATCC CCATTATTTT CAATCTGAAT TTCATTTTTT 240

TTTTTTAATT CATGAAATTT ATATGTCCCA CGTATTACTA CATATTTGCG TTTTTAATTA 300

AATAAATAAC TGTTACTTTT ATTATATCTT ATTTGCAGAT CACTTATCTG ATCAAATGTT 360

TTCGTTTTCG TGTGTGGTGA CGATGTATTA GGTACGCGAA ATAAACAAAA CAAACAAACA 420

AGGCCGCAAC AATAACATCA TCTAAAGACT TCCTTTGTGA CCCGCTTCTC AACAGCGGGT 480

GTAGAACTTA TGGTATGGCC AGAAAGTAAC GTTGAGTATA GATACAGAAG CAAGCAATTC 540

AAAGGAAAAA GTAATAAAAA GTATATAAAA GCGCAAAAAA TACAACAAGA AAGAATTTGT 600

TTGATGCCAG CGGAAAACCA AAATACGGGT CAAGATAGAA GCTCCAACAG CATCAGTAAA 660

AATGGCAACT CTCAGGTTGG ATGTCACACT GTTCCTAATG AGGAACTGAA CATCACTGTA 720

GCTGTGCGAT GCAGAGGAAG GAATGAAAGG GAAATTAGTA TGAAAAGCTC CGTTGTGGTA 780

AATGTTCCAG ATATTACAGG TTCTAAAGAA ATTTCCATTA ACACGACGGG AGATACCGGT 840

ATAACTGCTC AAATGAATGC CAAGAGATAC ACAGTGGACA AAGTCTTCGG TCCCGGCGCT 900

TCCCAGGATC TAATTTTTGA TGAAGTGGCG GGCCCATTAT TCCAGGATTT CATTAAAGGT 960

TACAATTGCA CCGTACTGGT ATATGGTATG ACGTCAACAG GTAAAACATA TACAATGACG 1020

GGCGACGAAA AGTTATATAA TGGTGAATTG AGCGATGCAG CAGGAATTAT ACCGAGGGTT 1080

CTTTTGAAGT TGTTTGACAC ATTGGAACTA CAACAGAACG ATTACGTAGT AAAATGTTCG 1140

TTCATTGAAC TCTACAACGA AGAATTGAAG GACCTCTTGG ACAGCAATAG CAACGGCTCT 1200

AGTAATACTG GCTTTGACGG CCAATTTATG AAAAAATTGA GGATTTTTGC TTCAAGCACA 1260

GCAAATAATA CCACTAGCAA CAGTGCTAGT AGTTCCAGGA GTAATTCTAG GAACAGTTCT 1320

CCGAGGTCAT TAAATGATCT AACACCTAAA GCTGCTCTAT TAAGAAAAAG GTTAAGGACA 1380

AAATCACTGC CGAATACCAT CAAGCAACAG TATCAACAAC AACAGGCAGT GAATTCCAGG 1440

AACAACTCTT CCTCTAACTC TGGCTCTACC ACTAATAATG CTTCTAGTAA CACCAACACA 1500

AATAACGGTC AAAGAAGTTC GATGGCTCCA AATGACCAAA CTAATGGTAT ATACATCCAG 1560

AATTTGCAAG AATTTCACAT AACAAATGCT ATGGAGGGGC TAAACCTATT ACAAAAAGGC 1620

TTAAAGCATA GGCAAGTAGC GTCCACTAAA ATGAACGATT TTTCCAGTAG ATCTCATACC 1680

ATTTTTACAA TCACTTTGTA TAAGAAGCAT CAGGATGAAC TATTTAGAAT TTCCAAAATG 1740

AATCTTGTGG ATTTAGCTGG TTCAGAAAAC ATCAACAGAT CCGGAGCATT AAATCAACGT 1800

GCCAAAGAAG CTGGTTCAAT CAACCAAAGT CTATTGACGC TGGGCAGGGT CATAAACGCA 1860

CTCGTAGATA AAAGCGGCCA TATACCTTTC CGTGAATCGA AATTGACCCG CCTGCTTCAA 1920

GATTCCCTGG GTGGTAATAC GAAAACCGCA CTAATTGCTA CTATATCGCC TGCAAAGGTA 1980

ACTTCTGAAG AAACCTGCAG TACATTAGAG TATGCTTCGA AGGCTAAAAA CATTAAGAAC 2040

AAGCCGCAAC TGGGTTCATT TATAATGAAG GATATTTTGG TTAAAAATAT AACTATGGAA 2100

TTAGCAAAGA TTAAATCCGA TTTACTCTCT ACAAAGTCCA AAGAAGGAAT ATATATGAGC 2160

CAAGATCACT ACAAAAATTT GAACAGTGAT TTAGAAAGTT ATAAAAATGA AGTTCAAGAA 2220

TGTAAAAGAG AAATTGAAAG TTTGACATCG AAAAATGCAT TGCTAGTAAA AGATAAATTG 2280

AAGTCAAAAG AAACTATTCA ATCTCAAAAT TGCCAAATAG AATCATTGAA AACTACCATA 2340

GATCATTTAA GGGCACAACT AGATAAACAG CATAAAACTG AAATTGAAAT ATCCGATTTT 2400

AATAACAAAC TACAGAAGTT GACTGAGGTA ATGCAAATGG CCCTACATGA TTACAAAAAA 2460

AGAGAACTTG ACCTTAATCA AAAGTTTGAA ATGCATATTA CTAAAGAAAT TAAAAAATTG 2520

AAATCTACAC TGTTTTTACA ATTAAACACT ATGCAACAGG AAAGTATTCT TCAAGAGACT 2580

AATATCCAAC CAAATCTTGA TATGATCAAA AATGAAGTAC TGACTCTTAT GAGAACCATG 2640

CAAGAAAAAG CTGAACTAAT GTACAAAGAC TGTGTGAAGA AAATTTTAAA CGAATCTCCT 2700

AAATTCTTCA ATGTTGTTAT TGAGAAAATC GACATAATAA GAGTAGATTT CCAAAAATTT 2760

TATAAAAATA TAGCCGAGAA TCTTTCTGAT ATTAGCGAAG AAAATAACAA CATGAAACAG 2820

TACTTAAAAA ACCATTTTTT CAAGAATAAC CATCAAGAAT TACTGAATCG TCATGTGGAT 2880

TCTACTTATG AAAATATTGA GAAGAGAACA AACGAGTTTG TTGAGAACTT TAAAAAGGTC 2940

CTAAATGACC ACCTTGACGA AAATAAAAAA CTAATAATGC ACAATCTGAC AACTGCAACC 3000

AGCGCGGTTA TTGATCAAGA AATGGATCTG TTTGAACCCA AGCGCGTTAA ATGGGAAAAT 3060

TCATTTGATC TGATAAATGA TTGTGACTCC ATGAATAACG AATTCTATAA TAGCATGGCA 3120

GCGACGCTAT CGCAAATCAA GAGTACTGTT GATACATCAT CAAATTCGAT GAATGAGTCT 3180

ATTTCAGTCA TGAAAGGACA AGTGGAAGAA TCGGAGAACG CTATATCCCT TTTGAAGAAC 3240

AATACCAAAT TTAATGATCA ATTTGAGCAG CTTATTAACA AGCATAACAT GTTGAAAGAT 3300

AACATTAAAA ATTCGATAAC ATCAACACAC TCTCATATAA CTAATGTGGA TGATATCTAT 3360

AATACGATTG AAAACATAAT GAAAAACTAT GGTAACAAGG AAAACGCTAC CAAAGACGAA 3420

ATGATCGAGA ACATATTGAA GGAAATACCA AATCTAAGTA AGAAAATGCC GTTAAGGTTA 3480

TCAAACATAA ATAGCAATTC AGTGCAAAGT GTAATATCGC CCAAAAAGCA TGCAATTGAA 3540

GATGAAAACA AATCCAGTGA AAATGTGGAC AATGAGGGCT CGAGAAAAAT GTTAAAGATT 3600

GAATAGTTGA TATTGCCTTT CAGTCGAATA TATATTCAAA CTAGTGGTTA ATAAAAACAA 3660

AGTATGTAAA GAATACTCAG TTATTCATTA GAAGGCAAGA CAGAAGAGAA GGGTGTGAAA 3720

CCACCTCTAC CAAACACACC AAGAGATGAA CCTAAATCAA ATTTTCACAG AGCTAACTAT 3780

ATAAACGTTT GGATTCGTGT GTACTATCTT TATTTACGGA AATAAGTTGT AATATTAAAA 3840

AAAAAAAAAA ACATTTTGAT GGACAATGAA TTTCTCTAAT TTT 3883

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

CGGGTGTAGG ATCCATGGTA TGGCCAGAAA GTAACG 36

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 53 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

GTGGACAATG GCGGCCGCAG AAAAAGGATC CAGATTGAAT AGTTGATATT GCC 53

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GAATATTCTA GAACAACTAT CAGGAGTC 28

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

TTGTCACTCG AGTGAAAAAG ACCAG 25

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3466 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

CTGCAGCAGA AAATCCAGTA GAACCATCAT CATGTTTGCT GTTTTTCGAT TTTTTCTTTC 60

TTGGGAAGTC GTCGTCCTCT TCTTCTTCAT CATCATCTTC TTCAGCATCA CTTTGTTCGT 120

TATCTATAAT TTTAGATGAT TCATCGCTAG AGCTATTCTG CTCGTCTTCT TCGGCTTCAT 180

CACCTTCCAT TATTGTATCT TTTTCCGGCT CATTACTTAA CTCTTGGTTG CCACTATTCC 240

TTTTTTCACG CCCAAATTCT GCATTCTTTC TGGTTCTTTT CTTATCCTTA GTGTCTACTC 300

TGTGCTTGGA GCCCATGATC AATTATGTAC TGATTTTCCT TCGGCTTCTC TATCGCTTTA 360

TTCATAGCAT CTGTTTATTA CCTTTCCTTA TATCTTATGG GCATCGAATC CTAGATTTTT 420

TTCTTTCAAA ATTTTCCAAT AAGAGGGTAA TGGAGATACA CCAAAATGAA TCTCAAACAA 480

AATCAAAACA AACACTGTTT ACAATTTGAT GCGCCTCGAA TCAAAATATG ATGATGAGTA 540

TTACAGCTAA AAAAATTATC GAATATTATA TAAGCATTAA AGCTATCAAT TTTTCCGCTC 600

TTTGTGTTTC TTATTATTCT ATTTGAATAT ACCAGAACAA CTATCCGGAG TCTTTGTTTA 660

AAAAAGGTAG ATTTTGAAAT AAAGGACTTA GAGAAATTCT GGCAACTATT AAAGTATGGA 720

ATCACTTCCA CGTACTCCCA CAAAAGGCAG ATCTACGCAG CATCTCTCGA CACCATCGCC 780

GAAGAATGAT ATTTTAGCTA TGAATGGCCA CAAAAGAAGA AATACAACAA CTCCACCGCC 840

TAAGCACACT CTTCTGAAGC CGCAACGTAC GGATATTCAT AGACACTCAT TAGCTAGTCA 900

GAGTCGCATA TCCATGTCAC CTAATCGCGA GCTTTTAAAG AATTATAAAG GTACAGCAAA 960

TTTGATTTAT GGAAACCAGA AAAGCAACTC CGGTGTAACT TCCTTTTATA AAGAAAATGT 1020

TAATGAACTC AATAGAACAC AAGCAATCTT ATTTGAGAAA AAGGCAACAC TAGATTTACT 1080

CAAAGATGAA CTAACAGAAA CGAAAGAGAA AATCAATGCC GTTAATCTCA AATTTGAAAC 1140

CCTTCGTGAA GAAAAGATAA AAATTGAACA GCAACTGAAT TTGAAAAACA ATGAACTTAT 1200

CTCGATTAAA GAAGAATTTT TGTCAAAGAA GCAGTTCATG AATGAAGGAC ATGAAATACA 1260

TTTAAAGCAG CTAGCGGCAT CTAATAAAAA AGAGCTGAAA CAAATGGAAA ATGAATACAA 1320

AACAAAAATT GAGAAATTGA AATTTATGAA GATTAAACAG TTTGAAAATG AAAGAGCGTC 1380

GCTTTTAGAT AAAATAGAAG AGGTAAGAAA TAAAATCACC ATGAACCCTT CCACTTTACA 1440

GGAAATGTTG AACGATGTTG AACAAAAGCA TATGCTTGAA AAAGAAGAAT GGCTTACAGA 1500

GTACCAATCG CAGTGGAAAA AGGATATAGA GCTGAATAAT AAACATATGC AAGAAATCGA 1560

AAGCATAAAA AAGGAAATCG AAAATACATT AAAACCTGAG TTGGCAGAAA AAAAGAAGCT 1620

CTTAACAGAA AAGCGTAACG CGTATGAAGC TATCAAAGTA AAAGTTAAAG AAAAGGAAGA 1680

GGAAACTACA AGGCTGAGAG ATGAGGTGGC ATTAAAACAG AAAACTAATT TAGAAACTTT 1740

GGAAAAGATC AAAGAACTTG AGGAATATAT AAAAGACACT GAACTGGGTA TGAAGGAGTT 1800

GAATGAAATT CTGATTAAAG AGGAAACGGT TAGACGCACA TTGCATAATG AGTTACAAGA 1860

GTTAAGAGGA AATATACGAG TTTATTGTAG GATTCGTCCA GCTCTAAAAA ATTTGGAAAA 1920

TTCTGATACT AGCCTTATTA ATGTTAATGA ATTTGATGAC AATAGTGGTG TTCAATCTAT 1980

GGAAGTGACG AAAATACAAA ACACAGCGCA AGTGCATGAA TTCAAATTTG ATAAAATATT 2040

TGATCAACAG GATACAAATG TGGATGTTTT TAAAGAAGTT GGTCAGTTAG TGCAAAGTTC 2100

ATTAGATGGA TATAATGTTT GTATCTTCGC ATACGGACAA ACAGGATCTG GGAAAACTTT 2160

CACGATGTTA AATCCAGGTG ATGGTATCAT TCCGTCCACA ATATCTCATA TATTTAACTG 2220

GATCAATAAA TTAAAGACAA AAGGATGGGA TTATAAAGTT AACTGCGAAT TCATTGAGAT 2280

CTACAACGAG AACATCGTAG ACTTATTGAG AAGTGATAAT AATAATAAAG AAGACACAAG 2340

CATTGGCTTA AAGCACGAAA TACGTCATGA TCAGGAAACT AAGACTACCA CGATAACGAA 2400

TGTTACGAGT TGCAAGCTTG AGTCGGAAGA AATGGTGGAA ATAATCCTGA AAAAAGCAAA 2460

TAAATTAAGA TCCACCGCTA GCACAGCATC AAATGAGCAT TCCTCCCGTT CACACAGTAT 2520

TTTCATAATT CATTTGTCTG GATCAAATGC AAAAACTGGA GCACACTCGT ATGGCACACT 2580

AAATCTTGTT GATTTGGCCG GTTCCGAAAG AATAAATGTC TCTCAAGTTG TAGGGGATAG 2640

ATTAAGAGAA ACACAAAATA TAAATAAATC TTTAAGTTGC TTAGGTGACG TTATTCATGC 2700

TTTAGGTCAG CCTGATAGTA CCAAAAGACA TATACCGTTC AGGAACTCAA AACTGACATA 2760

CCTACTGCAA TATTCACTCA CTGGGGATTC GAAAACATTA ATGTTTGTAA ACATTTCACC 2820

AAGCTCCTCT CATATTAATG AGACTCTCAA TTCGTTAAGA TTTGCGTCTA AAGTGAATTC 2880

TACCAGATTG GTTAGTAGAA AATGAGGTCA AGGCCTTTTC TGGTCTTTTT CACTCCTTTG 2940

ACAAATGACA GAGACTGTCC ATACATTCAT CACATGTAAC TATATTATAT ATGAAACTCA 3000

TTTTAATGCG CACAGATAAA AAGCAAAGTA AGTAATGAAT ATTTGTTATG TAAAAATGAC 3060

CTCATACATG CTAGTATTTA CACGAATTTA ATTGCTTAAA TTTCAATCAT CCTTACCCTT 3120

TGGTTTACCC TCTGGAGGCA GAAACTTTTG CATCCTCCTT ATTGCCCAAT TTTCGCCAAT 3180

GACTTTAACA TCTGGGTCCG ATTTACCTTC CGTGGTGTTG AACCGCTTCC ACCATGAGGG 3240

GGATTTGAAC CTAGGGTCTT CGCGTGGTAA TTTGCGAACT TCATTTCTAA TTTCAGCAAC 3300

ATGGGCTCTC AGTTCAGCGG CTAATCTGCT TCTTAAATCT TGCGCCTCTT TACCATATTT 3360

CAATTCGTCA GAGAGGTCGT TAGGATTTTT GGGATCATAG TATTTTTCAA CCAAATGTGT 3420

CCATTCTTTT CTATACCTGT CGATTAAATC ATCATTTAAA GGATCC 3466

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

GATAGTTAAG GATCCATGGC TCGTTCTTCC TTGCCCAACC GC 42

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

AAACTTCATC AATGCGGCCG CTAAGGGGAT CCAGCCATTG TAAAT 45

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2385 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

GAATTCCGAT AGTATTATGT GGAGTTCCAT TTTTATGTAT TTTTTGTATG AAATATTCTA 60

GTATAAGTAA ATATTTTATC AGAAGTATTT ACATATCTTT TTTTTTTTTA GTTTGAGAGC 120

GGCGGTGATC AGGTTCCCCT CTGCTGATTC TGGGCCCCGA ACCCCGGTAA AGGCCTCCGT 180

GTTCCGTTTC CTGCCGCCCT CCTCCGTAGC CTTGCCTAGT GTAGGAGCCC CGAGGCCTCC 240

GTCCTCTTCC CAGAGGTGTC GGGGCTTGGC CCCAGCCTCC ATCTTCGTCT CTCAGGATGG 300

CGAGTAGCAG CGGCTCCAAG GCTGAATTCA TTGTCGGAGG GAAATATAAA CTGGTACGGA 360

AGATCGGGTC TGGCTCCTTC GGGGACATCT ATTTGGCGAT CAACATCACC AACGGCGAGG 420

AAGTGGCAGT GAAGCTAGAA TCTCAGAAGG CCAGGCATCC CCAGTTGCTG TACGAGAGCA 480

AGCTCTATAA GATTCTTCAA GGTGGGGTTG GCATCCCCCA CATACGGTGG TATGGTCAGG 540

AAAAAGACTA CAATGTACTA GTCATGGATC TTCTGGGACC TAGCCTCGAA GACCTCTTCA 600

ATTTCTGTTC AAGAAGGTTC ACAATGAAAA CTGTACTTAT GTTAGCTGAC CAGATGATCA 660

GTAGAATTGA ATATGTGCAT ACAAAGAATT TTATACACAG AGACATTAAA CCAGATAACT 720

TCCTAATGGG TATTGGGCGT CACTGTAATA AGTGTTTAGA ATCTCCAGTG GGGAAGAGGA 780

AAAGAAGCAT GACTGTTAGT ACTTCTCAGG ACCCATCTTT CTCAGGATTA AACCAGTTAT 840

TCCTTATTGA TTTTGGTTTG GCCAAAAAGT ACAGAGACAA CAGGACAAGG CAACACATAC 900

CATACAGAGA AGATAAAAAC CTCACTGGCA CTGCCCGATA TGCTAGCATC AATGCACATC 960

TTGGTATTGA GCAGAGTCGC CGAGATGACA TGGAATCATT AGGATATGTT TTGATGTATT 1020

TTAATAGAAC CAGCCTGCCA TGGCAAGGGC TAAAGGCTGC AACAAAGAAA CAAAAATATG 1080

AAAAGATTAG TGAAAAGAAG ATGTCCACGC CTGTTGAAGT TTTATGTAAG GGGTTTCCTG 1140

CAGAATTTGC GATGTACTTA AACTATTGTC GTGGGCTACG CTTTGAGGAA GCCCCAGATT 1200

ACATGTATCT GAGGCAGCTA TTCCGCATTC TTTTCAGGAC CCTGAACCAT CAATATGACT 1260

ACACATTTGA TTGGACAATG TTAAAGCAGA AAGCAGCACA GCAGGCAGCC TCTTCCAGTG 1320

GGCAGGGTCA GCAGGCCCAA ACCCCCACAG GCAAGCAAAC TGACAAAACC AAGAGTAACA 1380

TGAAAGGTTA GTAGCCAAGA ACCAAGTGAC GTTACAGGGA AAAAATTGAA TACAAAATTG 1440

GGTAATTCAT TTCTAACAGT GTTAGATCAA GGAGGTGGTT TTAAAATACA TAAAAATTTG 1500

GCTCTGCGTT AAAAAAAAAA AAGACGTCCT TGGAAAATTT GACTACTAAC TTTAAACCCA 1560

AATGTCCTTG TTCATATATA TGTATATGTA TTTGTATATA CATATATGTG TGTATATTTA 1620

TATCATTTCT CTTGGGATTT TGGGTCATTT TTTTAACAAC TGCATCTTTT TTACTCATTC 1680

ATTAACCCCC TTTCCAAAAA TTTGGTGTTG GGAATATAAT ATAATCAATC AATCCAAAAT 1740

CCTAGACCTA ACACTTGTTG ATTTCTAATA ATGAATTTGG TTAGCCATAT TTTGACTTTA 1800

TTTCAGACTA ACAATGTTAA GATTTTTTAT TTTGCATGTT AATGCTTTAG CATTTAAAAT 1860

GGAAAATTGT GAACATGTTG TAATTTCAAG AGGTGAGTTT GGCATTACCC CCAAAGTGTC 1920

TATCTTCTCA GTTGCAGAGC ATCTCATTTT CTCTCTTAAA TGCTCAAATA AATGCAAAGC 1980

TCAGCACATC TTTTCTAGTC ACAAAAATAA TTCTTTTATT TGCAGTTTAC GTATGATCTT 2040

AATTTCAAAA CGATTTCTTT GTTTTTGGCT TGATTTTTCA CAATGTTGCA AATATCAGGC 2100

TCCCAGGGTT TAATGTGGAA TTGAAGTCTG CAGCCAGGCC TTGCAAATTG AAGGTAACTG 2160

GGGCAAATGC CATTGAAACC GCTAGTCTTA TTTCCTTTCT ACTTTTCTTT GGCACTCTTA 2220

CTGCCTGTAA GGAGTAGAAC TGTTAAGGCA CACTGTTGCT ATACAGTTAA CTCCCATTTT 2280

CATGTTTTGT CTTTCTTTTC CCATTTCTGG GGCTTACCTC CTGATACCTG CTTACTTTCT 2340

GGAAGTAGTG GGCAAGTAAG ATTTGGCTCT TGGTTTCTGG AATTC 2385

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 34 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

CTTCGTCTCT CACATATGGG CGAGTAGCAG CGGC 34

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3505 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

GAATTCCGAC AGGAAAGCGA TGGTGAAAGC GGGGCCGTGA GGGGGGCGGA GCCGGGAGCC 60

GGACCCGCAG TAGCGGCAGC AGCGGCGCCG CCTCCCGGAG TTCAGACCCA GGAAGCGGCC 120

GGGAGGGCAG GAGCGAATCG GGCCGCCGCC GCCATGGAGC TGAGAGTCGG GAACAGGTAC 180

CGGCTGGGCC GGAAGATCGG CAGCGGCTCC TTCGGAGACA TCTATCTCGG TACGGACATT 240

GCTGCAGGAG AAGAGGTTGC CATCAAGCTT GAATGTGTCA AAACCAAACA CCCTCAGCTC 300

CACATTGAGA GCAAAATCTA CAAGATGATG CAGGGAGGAG TGGGCATCCC CACCATCAGA 360

TGGTGCGGGG CAGAGGGGGA CTACAACGTC ATGGTGATGG AGCTGCTGGG GCCAAGCCTG 420

GAGGACCTCT TCAACTTCTG CTCCAGGAAA TTCAGCCTCA AAACCGTCCT GCTGCTTGCT 480

GACCAAATGA TCAGTCGCAT CGAATACATT CATTCAAAGA ACTTCATCCA CCGGGATGTG 540

AAGCCAGACA ACTTCCTCAT GGGCCTGGGG AAGAAGGGCA ACCTGGTGTA CATCATCGAC 600

TTCGGGCTGG CCAAGAAGTA CCGGGATGCA CGCACCCACC AGCACATCCC CTATCGTGAG 660

AACAAGAACC TCACGGGGAC GGCGCGGTAC GCCTCCATCA ACACGCACCT TGGAATTGAA 720

CAATCCCGAA GAGATGACTT GGAGTCTCTG GGCTACGTGC TAATGTACTT CAACCTGGGC 780

TCTCTCCCCT GGCAGGGGCT GAAGGCTGCC ACCAAGAGAC AGAAATACGA AAGGATTAGC 840

GAGAAGAAAA TGTCCACCCC CATCGAAGTG TTGTGTAAAG GCTACCCTTC CGAATTTGCC 900

ACATACCTGA ATTTCTGCCG TTCCTTGCGT TTTGACGACA AGCCTGACTA CTCGTACCTG 960

CGGCAGCTTT TCCGGAATCT GTTCCATCGC CAGGGCTTCT CCTATGACTA CGTGTTCGAC 1020

TGGAACATGC TCAAATTTGG TGCCAGCCGG GCCGCCGATG ACGCCGAGCG GGAGCGCAGG 1080

GACCGAGAGG AGCGGCTGAG ACACTCGCGG AACCCGGCTA CCCGCGGCCT CCCTTCCACA 1140

GCCTCCGGCC GCCTGCGGGG GACGCAGGAA GTGGCTCCCC CCACACCCCT CACCCCTACC 1200

TCACACACGG CTAACACCTC CCCCCGGCCC GTCTCCGGCA TGGAGAGAGA GCGGAAAGTG 1260

AGTATGCGGC TGCACCGCGG GGCCCCCGTC AACATCTCCT CGTCCGACCT CACAGGCCGA 1320

CAAGATACCT CTCGCATGTC CACCTCACAG ATTCCTGGTC GGGTGGCTTC CAGTGGTCTT 1380

CAGTCTGTCG TGCACCGATG AGAACTCTCC TTATTGCTGT GAAGGGCAGA CAATGCATGG 1440

CTGATCTACT CTGTTACCAA TGGCTTTACT AGTGACACGT CCCCCGGTCT AGGATCGAAA 1500

TGTTAACACC GGGAGCTCTC CAGGCCACTC ACCCAGCGAC GCTCGTGGGG GAAACATACT 1560

AAACGGACAG ACTCCAAGAG CTGCCACCGC TGGGGCTGCA CTGCGGCCCC CCACGTGAAC 1620

TCGGTTGTAA CGGGGCTGGG AAGAAAAGCA GAGAGAGAAT TGCAGAGAAT CAGACTCCTT 1680

TTCCAGGGCC TCAGCTCCCT CCAGTGGTGG CCGCCCTGTA CTCCCTGACG ATTCCACTGT 1740

AACTACCAAT CTTCTACTTG GTTAAGACAG TTTTGTATCA TTTTGCTAAA AATTATTGGC 1800

TTAAATCTGT GTAAAGAAAA TCTGTCTTTT TATTGTTTCT TGTCTGTTTT TGCGGTCTTA 1860

CAAAAAAAAT GTTGACTAAG GAATTCTGAG ACAGGCTGGC TTGGAGTTAG TGTATGAGGT 1920

GGAGTCGGGC AGGGAGAAGG TGCAGGTGGA TCTCAAGGGT GTGTGCTGTG TTTGTTTTGC 1980

AGTGTTTTAT TGTCCGCTTT GGAGAGGAGA TTTCTCATCA AAAGTCCGTG GTGTGTGTGT 2040

GTGCCCGTGT GTGGTGGGAC CTCTTCAACC TGATTTTGGC GTCTCACCCT CCCTCCTCCC 2100

GTAATTGACA TGCCTGCTGT CAGGAACTCT TGAGGCCCTC GGAGAGCAGT TAGGGACCGC 2160

AGGCTGCCGC GGGGCAGGGG TGCAGTGGGT GTTACCAGGC AAAGCACTGC GCGCTTCTTC 2220

CCCAGGAGGT GGGCAGGCAG CTGAGAGCTT GGAAGCAGAG GCTTTGAGAC CCTAGCAGGA 2280

CAATTGGGAG TCCCAGGATT CAAGGTGGAA GATGCGTTTC TGGTCCCTTG GGAGAGGACT 2340

GTGAACCGAG AGGTGGTTAC TGTAGTGTTT GTTGCCTTGC TGCCTTTGCA CTCAGTCCAT 2400

TTTCTCAGCA CTCAATGCTC CTGTGCGGAT TGGCACTCCG TCTGTATGAA TGCCTGTGGT 2460

TAAAACCAGG AGCGGGGCTG TCCTTGCCAC GTGCCAAGAC TAGCTCAGAA AAGCCGGCAG 2520

GCCAGAAGGA CCCACCCTGA GGTGCCAAGG AGCAGGTGAC TCTCCCAACC GGACCCAGAA 2580

CCTTCACGGC CAGAAAGTAG AGTCTGCGCT GTGACCTTCT GTTGGGCGCG TGTCTGTTGG 2640

TCAGAAGTGA AGCAGCGTGC GTGGGGCCGA GTCCCACCAG AAGGCAGGTG GCCTCCGTGA 2700

GCTGGTGCTG CCCCAGGCTC CATGCTGCTG TGCCCTGAGG TTCCCAGGAT GCCTTCTCGC 2760

CTCTCACTCC GCAGCACTTG GGCGGTAGCC AGTGGCCATG TGCTCCCAAC CCCAATGCGC 2820

AGGGCAGTCT GTGTTCGTGG GCACTTCGGC TGGACCCCAT CACGATGGAC GATGTTCCCT 2880

TTGGACTCTA GGGCTTCGAA GGTGTGCACC TTGGTTCTCC CTTCTCCTCC CCAGAGTTCC 2940

CCCGGATGCC ATAACTGGCT GGCGTCCCAG AACACAGTTG TCAACCCCCC CACCAGCTGG 3000

CTGGCCGTCT GTCTGAGCCC ATGGATGCTT TCTCAATCCT AGGCTGGTTA CTGTGTAAGC 3060

GTGTTGGAGT ACGGCGCCTT GAGCGGGTGG GAGCTGTGTG TTGAAGTACA GAGGGAGGTT 3120

GGGGTGGGTC AGAGCCGAGT TAAGAGATTT TCTTTGTTGC TGGACCCCTT CTTGAAGGTA 3180

GACGTCCCCC ACCCGGAGAG ACGTCGCGCT GTGGCCTGAA GTGGCGCAAG CTTGCTTTGT 3240

AAATATCTGT GGTCCCGATG TAGTGCCCAG AACGTTTGTG CGAGGCAGCT CTGCGCCCGG 3300

GTTCCAGCCC GAGCCTCGCC GGGTCGCGTC TTCGGAGTGC TTGTGACAGT CCTTGCCCAG 3360

TATCTAGTCC CCGTCGCCCC GTGCAGGAGA CGTAGGTAGG ACGTCGTGTC AGCTGTGCAC 3420

TGACGGCCAG TCTCCGAGCT GTGCGTTTGT ATCGCCACTG TATTTGTGTA CTTTAACAAT 3480

CGTGTAAATA ATAAATTCGG AATTC 3505

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

CGCGGATCCT AATGGAGGTG AGAGTCGGG 29

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

CGCGGATCCG CTCATCGGTG CACGACAGA 29

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

GGAATCACTA CAGGGATG 18

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

ATTCTAGACA TGGAGACCAG TTCTTTTGAG 30

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

TGGAAGCTTA TATTACCATA GATTCTTCTT G 31

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

Ser Leu Ser Phe Pro Arg Gly Lys Ile Ser Lys Asp Glu Asn Asp Ile
1 5 10 15

Asp Cys Cys Ile Arg Glu Val Lys Glu Glu Ile Gly Phe Asp Leu Thr
20 25 30

Asp

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

Arg Trp Asn Gly Phe Gly Gly Tyr Val Gln Glu Gly Glu Thr Ile Glu
1 5 10 15

Asp Gly Ala Arg Arg Glu Leu Gln Glu Glu Ser Gly Leu Thr Val Asp
20 25 30

Ala

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

Lys Leu Glu Phe Pro Gly Gly Lys Ile Glu Met Gly Glu Thr Arg Glu
1 5 10 15

Gln Ala Val Val Arg Glu Leu Gln Glu Glu Val Gly Ile Thr Pro Gln
20 25 30

His

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

Asp Ile Ile Phe Pro Gly Gly Leu Pro Lys Asn Glu Glu Asp Pro Ile
1 5 10 15

Met Cys Leu Ser Arg Glu Ile Lys Glu Glu Ile Asn Ile Asp Ser Lys
20 25 30

Asp

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

Asp Ile Ile Phe Pro Gly Gly Leu Pro Lys Asn Glu Glu Asp Pro Ile
1 5 10 15

Met Cys Leu Ser Arg Glu Ile Lys Glu Glu Ile Asn Ile Asp Ser Lys
20 25 30

Asp

WHAT IS CLAIMED IS:

1. A method for isolating a polynucleotide encoding a protein that binds to a CKI isoform comprising the steps of:

a) transforming or transfecting appropriate host cells with a DNA construct comprising a reporter gene under the control of a promoter regulated by a transcription factor having a DNA-binding domain and an activating domain;

b) expressing in said host cells a first hybrid DNA sequence encoding a first fusion of part or all of a CKI isoform and either the DNA-binding domain or the activating domain of said transcription factor:

c) expressing in said host cells a library of second hybrid DNA sequences encoding second fusions of part or all of putative CKI isoform-binding proteins and either the DNA-binding domain or activating domain of said transcription factor which is not incorporated in said first fusion;

d) detecting binding of CKI isoform-binding proteins to said CKI isoform in a particular host cell by detecting the production of reporter gene product in said host cell; and

e) isolating second hybrid DNA sequences encoding CKI isoform-binding protein from said particular host cell.

2. The method of claim 1 wherein said CKI isoform is *S. cerevisiae* HRR25.

3. The method of claim 1 or 2 wherein said promoter is the ADHI promoter, said DNA-binding domain is the *lexA* DNA-binding domain, said activating domain is the GAL4 transactivation domain, said reporter gene is the *lacZ* gene and said host cell is a yeast host cell.

4. A method for detecting proteins which bind to a CKI isoform comprising the steps of:

a) transforming or transfecting appropriate host cells with a hybrid DNA sequence encoding a fusion between a putative CKI isoform-binding protein and a ligand capable of high affinity binding to a specific counterreceptor;

b) expressing said hybrid DNA sequence in said host cells under appropriate conditions;

c) immobilizing fusion protein from said host cells by exposing the fusion protein to said specific counterreceptor in immobilized form;

d) contacting a CKI isoform with said immobilized fusion protein; and

e) detecting said CKI isoform bound to said fusion protein using a reagent specific for said CKI isoform.

5. The method of claim 4 wherein the CKI isoform is *S. cerevisiae* HRR25.

6. The method of claim 4 or 5 wherein said ligand is glutathione-S-transferase and said counterreceptor is glutathione.

7. The method of claim 4 or 5 wherein said ligand is hemagglutinin and said counterreceptor is a hemagglutinin-specific antibody.

8. The method of claim 4 or 5 wherein said ligand is polyhistidine and said counterreceptor is nickel.

9. The method of claim 4 or 5 wherein said ligand is maltose-binding protein and said counterreceptor is amylose.

10. A purified and isolated polynucleotide encoding the TIH1 amino acid sequence set out in SEQ ID NO: 3.

11. The polynucleotide of claim 10 which is a DNA.

12. The DNA of claim 10 which is a cDNA.

13. The DNA of claim 10 which is a genomic DNA.

14. The DNA of claim 10 which is a chemically synthesized DNA.

15. A full length purified and isolated TIH1-encoding polynucleotide selected from the group consisting of:

a) the DNA set out in SEQ ID NO: 2, and

b) a DNA which hybridizes under stringent conditions to the protein coding portion of the DNA of a).

16. A purified and isolated TIH1 polynucleotide comprising the TIH1 DNA sequence set out in SEQ ID NO: 2.

17. A DNA expression construct comprising a DNA according to claim 11, 15 or 16.

18. A host cell transformed with a DNA according to claim 11, 15 or 16.

19. A method for producing an TIH1 polypeptide comprising growing a host cell according to claim 18 in a suitable medium and isolating TIH1 polypeptide from said host cell or the medium of its growth.

20. Purified and isolated TIH1 polypeptide consisting essentially of the TIH1 amino acid sequence set out in SEQ ID NO: 3.

21. An antibody capable of specifically binding to TIH1.

22. An antibody according to claim 21 which is a monoclonal antibody.

23. A hybridoma cell line producing a monoclonal antibody according to claim 22.

24. A purified and isolated polynucleotide encoding the TIH2 amino acid sequence set out in SEQ ID NO: 5.

25. The polynucleotide of claim 24 which is a DNA.

26. The DNA of claim 24 which is a cDNA.

27. The DNA of claim 24 which is a genomic DNA.

28. The DNA of claim 24 which is a chemically synthesized DNA.

29. A full length purified and isolated TIH2-encoding polynucleotide selected from the group consisting of:

a) the DNA set out in SEQ ID NO: 4, and

b) a DNA which hybridizes under stringent conditions to the protein coding portion of the DNA of a).

30. A purified and isolated TIH2 polynucleotide consisting essentially of TIH2 DNA sequence set out in SEQ ID NO: 4.

31. A DNA expression construct comprising a DNA according to claim 25.

32. A host cell transformed with a DNA according to claim 25.

33. A method for producing an TIH2 polypeptide comprising growing a host cell according to claim 32 in a suitable medium and isolating TIH2 polypeptide from said host cell or the medium of its growth.

34. Purified and isolated TIH2 polypeptide consisting essentially of the TIH2 amino acid sequence set out in SEQ ID NO: 5.

35. An antibody capable of specifically binding to TIH2.

36. An antibody according to claim 35 which is a monoclonal antibody.

37. A hybridoma cell line producing the monoclonal antibody according to claim 36.

38. A purified and isolated polynucleotide encoding the TIH3 amino acid sequence set out in SEQ ID NO: 7.

39. The polynucleotide of claim 38 which is a DNA.

40. The DNA of claim 38 which is a cDNA.

41. The DNA of claim 38 which is a genomic DNA.

42. The DNA of claim 38 which is a wholly or partially chemically synthesized DNA.

43. A full length purified and isolated TIH3 encoding polynucleotide selected from the group consisting of:

a) the DNA set out in SEQ ID NO: 6, and

b) a DNA which hybridizes under stringent conditions to the protein coding portion of the DNA of a).

44. A purified and isolated TIH3 polynucleotide consisting essentially of TIH3 protein coding sequence set out in SEQ ID NO: 6.

45. A DNA expression construct comprising a DNA according to claim 39.

46. A host cell transformed with a DNA according to claim 39.

47. A method for producing an TIH3 polypeptide comprising growing a host cell according to claim 46 in a suitable medium and isolating TIH3 polypeptide from said host cell or the medium of its growth.

48. Purified and isolated TIH3 polypeptide consisting essentially of the TIH3 amino acid sequence set out in SEQ ID NO: 7.

49. An antibody capable of specifically binding to TIH3.

50. An antibody according to claim 49 which is a monoclonal antibody.

51. A hybridoma cell line producing the monoclonal antibody according to claim 50.

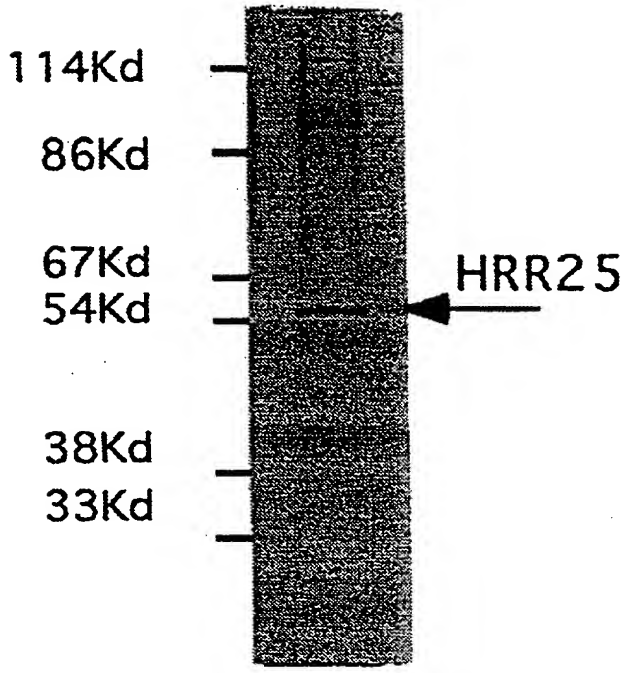

FIGURE 1

FIGURE 2

yeast TIH1	SLSFPRGKISKDENDIDCCIREVKEEIGFDLTD	(SEQ ID NO: 49)
human Hum8ODP	RWNGFGGKVQEGETIEDGARRELQEESGLTVDA	(SEQ ID NO: 50)
E.coli MutT	KLEFPGGKIEMGETREQAVVRELQEEVGITPQH	(SEQ IN NO: 51)
viral C11	DIIFPGGLPKNEEDPIMCLSREIKEEINIDSKD	(SEQ ID NO: 52)
viral VD10	DIIFPGGLPKNEEDPIMCLSREIKEEINIDSKD	(SEQ ID NO: 53)

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/US 95/00912

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K14/395 C12N9/12 C12N15/10 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YEAST, vol. 9, 1993 pages 1355-1371, SCHERENS, B. ET AL. 'Yeast sequencing reports' * page 1363, sequence YBL0506 * ---	24-37
Y	SCIENCE, vol. 253, 1991 pages 1031-1034, HOEKSTRA, M.F. ET AL. 'HRR25, a putative protein kinase from budding yeast: Association with repair of damaged DNA' cited in the application * whole disclosure * --- -/--	1-9

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 June 1995	27.06.95

Name and mailing address of the ISA	Authorized officer
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Int onal Application No
PCT/US 95/00912

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SCIENCE, vol. 257, 1992 pages 680-682, YANG, X. ET AL. 'A protein kinase substrate identified by the two hybrid system' cited in the application * whole disclosure * ---	1-3
Y	CHEMICAL ABSTRACTS, vol. 109, no. 1, 4 July 1988 Columbus, Ohio, US; abstract no. 2855a, FIELD, J. ET AL. 'Purification of a RAS-responsive adenylyl cyclase complex ...' page 275; cited in the application see abstract & MOL. CELL. BIOL., vol. 8,no. 5, 1988 pages 2159-2165, -----	4-9

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